Post-polypectomy surveillance colonoscopy: In whom and when?

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Abstract

Introduction

Post-polypectomy surveillance by colonoscopy is recommended in national and international guidelines. While colonoscopy is the gold standard colorectal investigation, it carries a risk of adverse events as well as being inconvenient and often uncomfortable for the patient.

It is established that population screening reduces mortality from colorectal cancer (CRC). The effect of post-polypectomy surveillance, however, is less clear. An increasing number of colonoscopies are being performed worldwide for both symptoms and screening. The adenoma detection rate at colonoscopy is also increasing with improved technology and training against the backdrop of an ageing population. As a result, an increasing number of individuals are entering post-polypectomy surveillance.

Aims & Objectives

The aim of the analysis was to evaluate the findings of post-polypectomy surveillance within the English Bowel Cancer Screening Programme (BCSP). This was done by assessing linked data from the BCSP database and the National Cancer Registration and Analysis Service (NCRAS). Objectives were:

1. To document surveillance pathways among the intermediate and high risk groups.

2. To determine the risk factors (adenoma and person-specific) at screening which predict the outcome of initial surveillance.
3. To determine the adenoma, advanced adenoma (AA) and CRC yield at initial surveillance of each colonoscopy surveillance cohort (and subcategories within each cohort) within the BCSP.

Methods

Data on individuals participating in the BCSP is entered prospectively onto the screening programme's relational database, BCSS. BCSS was interrogated for individuals who had attended for post-polypectomy surveillance at any time from the start of the programme in 2006 until the end of 2016. In addition, linked data on CRCs diagnosed in this cohort were obtained from NCRAS.

Two separate analyses were performed. The first focussed on the detection of any AA (size ≥10mm or ≥25% villous or high-grade dysplasia) at the first surveillance attended by an individual. A separate analysis was performed with a diagnosis of CRC as the primary outcome.

Results

Of individuals with high risk findings at baseline colonoscopy, 12.3% of those attending first surveillance were found to have AA, 48.0% non-advanced adenoma, 39.1% no adenoma, and 0.5% CRC.

In the case of individuals with intermediate risk findings at baseline, of those attending first surveillance, 8.0% were found to have AA, 35.3% non-advanced

adenoma, 56.1% no adenoma, and 0.4% CRC. In those categorised as intermediate risk based on the finding of a single adenoma (≥10mm) at baseline, 6.3% of those attending first surveillance were found to have AA and 0.3% CRC.

The most significant factor increasing the risk of AA at first surveillance was a higher total number of adenomas at baseline colonoscopy.

Conclusions

The rates of AA and CRC at first surveillance are relatively low and were found to be higher in the high risk group compared to intermediate risk. Those individuals categorised as intermediate risk based on a single adenoma (≥10mm) at baseline, had a particularly low rate of AA and CRC at first surveillance.

These findings support the hypothesis that the incidence of AA and CRC are low at post-polypectomy surveillance colonoscopy. The particularly low yield in the subgroup with a single adenoma at baseline suggests that surveillance is not be needed in this group and may not be necessary for the intermediate risk cohort as a whole.

Authorship note

The contribution of Professor Linda Sharp, who helped to perform the statistical analyses, is formally acknowledged.

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Ethical approval was granted by the University of Durham ethics committee for all work undertaken in this thesis. I confirm that no part of the material offered has previously been submitted by me for a degree in this or any other university. All material from the work of others has been referenced accordingly with no copyright infringements.

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Publications

Oral presentation:

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Bonnington S, Sharp L, Rutter M. Post-polypectomy surveillance in the English bowel cancer screening programme: Multivariate logistic regression of factors influencing advanced adenoma detection at first surveillance. *ESGE Days, Prague, Czech Republic, April 2019.*

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Journal publication:

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Glossary

AA: advanced adenoma: a colorectal adenoma possessing at least one of three features: high grade dysplasia, villous architecture, or size ≥10mm.

ASA: American Society of Anaesthesiologists grade (of physical health based on presence of pre-existing health conditions)

BCSP: Bowel Cancer Screening Programme (in England)

BCSS: Bowel Cancer Screening System

CRC: colorectal cancer

EMR: endoscopic mucosal resection

Episode: an episode of investigation within the BCSP: one or more diagnostic test and the associated therapeutic procedures (e.g. polypecomy). An episode may be either screening (index episode after a positive FOBt) or surveillance.

ESD: endoscopic submucosal dissection

FAP: familial adenomatous polyposis

FOBt: (guiac) faecal occult blood test

HR: High Risk; the outcome of an episode of investigation based on the number and size of adenomas

ICC: interval colorectal cancers

IR: Intermediate Risk; the outcome of an episode of investigation based on the number and size of adenomas

MAP: MUTYH-associated polyposis

MDM: multidisciplinary team meeting

MVA: multivariate analysis

NCRAS: National Cancer Registration and Analysis Service

PCCRC: post-colonoscopy colorectal cancer

Screening episode: the index episode of investigation in the BCSP following a positive FOBt

SPS: Serrated polyposis syndrome

SSP: specialist screening practitioner (trained nurse)

Surveillance episode: an episode in the BCSP performed for the purpose of surveillance after at least one previous polypectomy

VIF: Variance Inflation Factor (statistical test)

Contents

CHAPTER 1 - Introduction

The aim of this thesis was to address the clinical utility of post-polypectomy surveillance colonoscopy. Evidence in the published literature was synthesised in a systematic review. Data from the BCSP were analysed in depth to investigate the outcome of an organised surveillance programme over a period of greater than ten years.

The research question addressed was to quantify the incidence of both colorectal cancer and advanced adenoma at post-polypectomy surveillance; to define the findings at baseline which confer a lower risk of advanced neoplasia at surveillance, and thereby identify individuals who do not require surveillance.

Background

Colorectal cancer (CRC) is the second leading cause of death from cancer in the UK[1] and USA[2]. Over 41,000 people in the UK are diagnosed with CRC annually and over 16,000 people die of the disease.

First described in 1984, the adenoma-carcinoma sequence details the development of colorectal cancer from its precursor lesion: the colorectal adenoma. It is widely accepted that the majority of colorectal cancers develop

from adenomas and that this occurs over a timeframe of several years. Such a natural history presents an opportunity for prevention of malignancy through detection and removal of colorectal adenomas.

During the 21st century, population-based colorectal cancer screening programmes have been introduced in many countries around the world. Each programme differs in its approach. There are a number of screening modalities available with varying characteristics such as diagnostic accuracy, cost, and acceptability to patients. Colonoscopy is the gold standard investigation of the colorectum, with high sensitivity and specificity for adenomas and cancers. However, colonoscopy requires significant financial and resource expenditure as well as carrying a small risk of serious complications and potential discomfort and inconvenience for the patient. Despite this, many countries including the USA, Poland, and Germany, advocate primary screening colonoscopy.

Alternative screening strategies may involve an alternative test or a combination of investigations. Faecal tests include the guaiac-based faecal occult blood (FOBT) or the faecal immunohistochemical test (FIT). Sigmoidoscopy and virtual CT colonography are also used.

In England, the Bowel Cancer Screening Programme (BCSP) began in 2006. Men and women aged 60 are invited to complete an FOBT which, if positive,

results in an invitation for colonoscopy. The FOBT is repeated biennially and continued to age 69 in the early years of the programme, but is now continued to age 74.

In 2013, a new screening modality was added to the BCSP with a one-off sigmoidoscopy being offered to 55 year olds. This programme, known as "Bowel Scope Screening" is in addition to the existing FOBT testing for 60-74 year olds.

Screening programmes aim to reduce the incidence and mortality from CRC by removal of adenomas and detection of cancers at an earlier, potentially curable stage. For some individuals in whom adenomas are detected and removed, there is an increased risk of CRC compared to individuals with no adenomas. This is the rationale for post-polypectomy surveillance colonoscopy. However, there is little evidence for the effectiveness of post-polypectomy surveillance and an effect on CRC mortality is unproven.

The English Bowel Cancer Screening Programme is recognised internationally as an exemplar for quality in colonoscopy. All colonoscopies are performed by experienced endoscopists who are assessed prior to performing procedures within the programme and subsequently monitored to ensure ongoing high quality examinations. It is a peculiarity to the BCSP that surveillance colonoscopies are performed within the screening programme, not on general

endoscopy lists. Therefore, high quality examinations are performed at the index screening procedure as well as at surveillance colonoscopies.

The quality of examination by colonoscopy is paramount when considering effects on CRC incidence and mortality. While colonoscopy is the most sensitive investigation for both adenomas and carcinomas of the colorectum, sensitivity is not 100%: lesions may be missed. The protection against CRC and CRC-related mortality afforded by colonoscopy relies on the detection of colorectal lesions. When adenomas are detected in a lower proportion of colonoscopies, there is a higher rate of CRC in the years following the colonoscopy. These cases of cancer are termed post-colonoscopy colorectal cancers, or PCCRC, and are the key indicator of the success of colonoscopy in protecting against CRC.

As cases of PCCRC are relatively unusual, surrogate measures of quality are used to compare endoscopists, endoscopy units, and screening programmes. The proportion of colonoscopies in which at least one adenoma if found is termed the adenoma detection rate, ADR. This metric has become the standard quality metric in many screening programmes. A lower ADR has been shown to correlate with a higher rate of subsequent CRC[3].

Quality in colonoscopy has improved rapidly in recent years and in the UK has been driven largely by the BCSP. Current clinical guidelines are based on

evidence from the era before widespread screening programmes and high quality colonoscopy. Particularly with reference to surveillance recommendations, this change is fundamental. Where a higher ADR is achieved, a higher proportion of those adenomas present at the time of colonoscopy will be found and removed. Therefore, the ongoing future risk of neoplasia is reduced. However, because more adenomas have been found and documented, the patient will be categorised in a higher risk group and so offered surveillance at a shorter time interval. This concept is known as the "high detector" paradox.

New evidence from the modern era of high quality colonoscopy is therefore needed to inform clinical decisions on appropriate surveillance.

Together, the findings of this thesis provide a robust basis on which to change current clinical practice in the field of post-polypectomy surveillance. These findings have significant implications for the Bowel Cancer Screening Programme in England.

Setting

During time Out of Programme (OOP) from my gastroenterology training, I have been working as an endoscopy fellow at North Tees and Hartlepool NHS Foundation Trust. The Trust has a strong track record in clinical research,

particularly in gastroenterology. The Tees Bowel Cancer Screening Centre is based at the Trust and has been at the forefront of rolling out each stage of the Bowel Cancer Screening Programme.

The north east is recognised as a leading region of England in endoscopy research. Regional collaboration is facilitated through the Northern Region Endoscopy Group (NREG). The group has developed and delivered large studies of great clinical importance including DISCARD, QIC, and ADENOMA. During my clinical work in the past three years, I have had the opportunity to take part in two further regional trials, WASh and B-ADENOMA, as a trial endoscopist.

This thesis was written at the School of Medicine, Pharmacy and Health, Durham University and North Tees and Hartlepool NHS Foundation Trust.

Thesis structure

By way of introduction to the topic, this thesis opens with a narrative literature review. The main studies which follow comprise: a systematic review of surveillance in intermediate and high risk subjects, and a data analysis of Bowel Cancer Screening Programme data including multivariable analyses of factors conferring higher risk.

CHAPTER 2 – A resume of the literature: overall view

Colorectal cancer (CRC) is the second leading cause of death from cancer in the UK[1] and USA[2]. Over 41,000 people in the UK are diagnosed with CRC annually and over 16,000 people die of the disease.

Recognised risk factors for the development of CRC include advancing age, a personal or family history of CRC, longstanding inflammatory bowel disease affecting the colon, and specific conditions such as familial adenomatous polyposis (FAP), and hereditary non-polyposis colon cancer (HNPCC). This thesis will focus on an important risk factor for the development of CRC: a personal history of colorectal adenomas.

Some colonic polyps such as adenomatous and serrated polyps carry malignant potential, while others do not (hyperplastic, post-inflammatory, hamartomatous). This thesis will discuss only those polyps with malignant potential.

The majority of CRCs arise from colonic adenomas. Adenomas arise following aberrant proliferation of epithelial cells in the colon. These lesions may then progress to varying degrees in size and dysplasia[4]. Adenomas represent the

major precursor for CRC both in high-risk groups such as patients with a family history of familial adenomatous polyposis (FAP) or hereditary non-polyposis colorectal cancer (HNPCC), as well as in the general population. This concept is termed the "adenoma-carcinoma sequence"[5-9].

However, 20-30% of colorectal cancers arise through a different molecular pathway to the conventional adenoma-carcinoma sequence. These CIMP-positive cancers (CpG island methylator phenotype) are believed to arise from serrated polyps. Such lesions are over-represented among "interval cancers" (cancers diagnosed 6-36 months after a colonoscopy)[10]. Growing evidence points to the importance of recognising and managing serrated lesions in preventing CRC [11].

The speed of progression along the pathway of proliferation and dysplasia is a key factor in determining clinical practice in patients found to have colonic adenomas. Progression from adenoma to invasive cancer can occur in five years or take more than 20 years[12]. Additionally, progression along this pathway is highly variable: one study estimates that only 0.25% of adenomas per year will progress to cancer[13]: some stabilise and some regress [12,14-16].

Adenoma prevalence in Western screening populations (age 50–75 years) can be as high as 40%, with advancing age and male sex associated with higher prevalence. However, lifetime risk of CRC is only 5.5% due to the highly

variable progression of adenomas[17-23]. Overall, projections of 10-year cumulative risk for progression from adenoma to carcinoma are less than 10%[16,24].

Risk factors

In recent years, an understanding of adenoma features predicting risk of progression to cancer has led to the term "advanced adenoma"[16], referring to adenomas possessing at least one of three high risk characteristics: size of at least 10mm, villous architecture of at least 25%, or high grade dysplasia[25-27]. Overall, these lesions progress to cancer at an annual rate of up to five percent: significantly higher than the average rate for all adenomas[13], and this risk increases with age to 25% at age 55 years and to 40% at age 80 years. Annual rates of progression from adenoma to carcinoma also vary depending on which of these advanced features is present. Size of at least 10mm confers a three percent annual risk; villous architecture 17%, and high grade dysplasia 37%[13].

As these figures illustrate, high grade dysplasia (HGD) confers high risk of progression to cancer. However, in keeping with the adenoma-carcinoma sequence described previously, high grade dysplasia is more likely to be found in larger lesions: as adenomas progress in size, so too dysplasia progresses[28]. The number of adenomas possessing advanced features (HGD or > 25% villous

architecture) increases with polyp size from approximately 1%-2% in diminutive adenomas (< 5 mm) to 7%-12% for small adenomas (5 to 9 mm) and 20%-30% for large adenomas (≥ 10 mm) [25,29,30]. Advancing age of the patient also increases the likelihood of HGD within an adenoma, independent of polyp size and histological type[31].

Most adenomas detected at colonoscopy (60%-75%) are smaller than 10mm diameter[32]. Larger adenomas of at least 10mm in diameter are at higher risk of containing CRC and are also a risk factor for metachronous cancer development (i.e. a cancer diagnosed at least 6 months after the index procedure)[25]. The absolute risk of metachronous advanced adenomas is close to 20% in patients whose largest baseline adenoma is 20mm or more in size[33].

The risk factor most closely correlating to CRC risk is the total number of adenomas, both at index procedure and cumulatively over the individual's lifetime. Patients with one or two small tubular adenomas removed do not have a significantly increased metachronous colorectal cancer risk[34]. In contrast, the presence of one or more advanced adenomas predicts a higher rate of both any and advanced metachronous adenomas[26]. The risk of metachronous CRC increases with the number of advanced adenomas[25]. Large polyp size (≥10mm) and proximal location in the colon are independent predictors of further advanced neoplasia at follow-up[35]. The risk for metachronous advanced adenomas increases progressively with the number

of adenomas at baseline examination: patients with only 1 adenoma have a risk of 9% while those with 5 or more adenomas have a 24% risk.

Benefit of colonoscopy

Colonoscopic screening has been shown to be effective in reducing CRC incidence and mortality[28,36-39].

This effect is via a number mechanisms. Firstly, the removal of pre-cancerous lesions, i.e. adenomatous polyps, thereby interrupting the progression to carcinoma: preventing cancers. Secondly, detection of CRC at an earlier, pre-symptomatic stage with resultant increased likelihood of successful endoscopic or surgical treatment[28,40-42].

The third mechanism, which may reduce CRC incidence and mortality, is surveillance colonoscopy. Risk stratification based upon index colonoscopy findings allows patients with polyps at higher risk of progression to cancer to be offered a further examination in the future [20,21,43]. The evidence for the potential benefits of surveillance will be discussed in detail later.

Patients diagnosed with CRC at an earlier stage have significantly better prognosis than those diagnosed with more extensive disease. Of patients diagnosed with Dukes' A CRC, 93% will survive 5 years. Those diagnosed with

modified Dukes' D cancer however, have a less than 7% chance of living a further 5 years.

Colonoscopy is considered to be the gold standard for adenoma detection and affords an opportunity for therapy, through polypectomy, as well as allowing histological diagnosis. Double-contrast barium enema and CT colonography (CTC) show poorer sensitivity compared to colonoscopy, particularly with respect to very small and flat polyps[44,45]. An optimally performed double-contrast barium enema and FIT (faecal immunohistochemical test) detect only half of adenomas of 5mm or larger that are detected by colonoscopy[46].

Limitations of colonoscopy

However, there remain limitations to colonoscopic screening. Even colonoscopy does not allow detection of all adenomas. "Back-to-back" colonoscopies have indicated significant miss rates of 27% for small adenomas (<5mm) and 6% for adenomas of more than 10mm diameter [47]. Studies performing both CTC and colonoscopy estimate that the colonoscopy miss rate for polyps over 10mm in size may be as high as 12%[48]. There are multiple factors likely to contribute to missed polyps at colonoscopy including quality of bowel preparation, and the training and experience of the colonoscopist. The time taken by colonoscopists during withdrawal of the colonoscope from the caecum is a powerful predictor of adenoma detection rate (ADR)[49]. Higher

rates of interval cancers are seen in association with low ADR at screening colonoscopy[3,50].

The protection afforded by colonoscopy is significantly greater in respect of distal CRC as compared to lesions of the proximal colon. There are a number of factors postulated to explain this differential: poorer right-sided bowel preparation, incomplete colonoscopy, anatomical factors impeding visibility, and potentially different biology of right-sided lesions, especially via the serrated pathway[36,51].

Incomplete resection of adenomatous tissue is believed to be a substantial contributor to interval cancers. Rates of incomplete resection for diminutive polyps are 29% for conventional biopsy and 17% for hot biopsy[52,53]. Residual polyp tissue is more likely to remain after resection of sessile polyps and risk increases with polyp size. Rates of 17% for polyps of 10-20mm and 7% for lesions of 5-9mm have been quoted. There also appears to be a higher rate of incomplete resection for serrated lesions in comparison to conventional adenomas (31% and 7% respectively)[54].

Missed lesions are likely to account for more than half of interval cancers diagnosed at 3 to 5 years after the index procedure[55]. Therefore, the quality of the index and subsequent colonoscopies is paramount in maximising the

potential benefit of surveillance procedures. Quality of colonoscopy is directly associated with rates of interval CRC[50].

Rationale for surveillance

The major CRC mortality risk reduction is achieved at index colonoscopy, i.e. diagnosis of cancers at an earlier stage and removal of adenomas with the aim of reducing CRC incidence.

Individuals found to have colonic polyps are at increased risk of advanced neoplasia in the future[12,24,56,57]. This risk may be due to a number of mechanisms:

1. Missed lesions at the initial colonoscopy,
2. Incomplete removal of adenomatous tissue at initial colonoscopy,
3. The individual's propensity to colonic neoplasia (either lifestyle factors, an inherent imbalance of cell proliferation, or a combination of these)[26,47,57-60].

In view of the increased risk of CRC, it seems logical that this group may benefit from closer monitoring than the general population. There are two reasons to consider surveillance colonoscopy in patients found to have adenomas at the index procedure. Firstly, as discussed above, there may be missed lesions, particularly small polyps, which may be identified at a

subsequent procedure. Secondly, after a time interval, new lesions may have developed.

Although the risk of developing further adenomas is known, no randomised study has directly assessed the effect of post-polypectomy surveillance on CRC incidence or mortality. The efficacy of surveillance has been assessed by retrospective epidemiological series indicating that patients not entered into a surveillance programme have three- to fourfold greater risk of CRC. However, the increased risk pertains to those found to have advanced adenomas at the index procedure. Individuals with non-advanced adenomas did not have significantly higher risk than the general population[24,60].

It is established that individuals with previously identified adenomas have an increased risk of further adenomas at a follow-up examination. At 4 year interval, 35.5% of patients will again be found to have at least one adenoma, but only 8.6-12% will have advanced neoplasia (either an advanced adenoma or carcinoma) with 0.6% having carcinoma. Factors conferring higher risk of further adenomas at surveillance are age greater than 60 years, male sex, and the presence of more than one adenoma at the initial procedure. The finding of more than 2 adenomas at initial examination increases the risk of advanced neoplasia at follow-up examination[33,61].

Stratification

Reported prevalence of adenomas ranges from 15-40%, with advancing age and male sex associated with increasing prevalence. However, rates of adenoma detection may be as high as 50% in the general population when using modern high definition endoscopes[62,63]. Therefore the number of patients who could potentially be offered surveillance colonoscopy is substantial.

To avoid unnecessary, or "low yield", surveillance colonoscopies, it is necessary to identify those individuals with increased risk of CRC. This can be achieved through a risk stratification approach, as adopted by all the major current clinical guidelines.

Current guidelines vary in their definition of each risk group. However, there is consensus that individuals with one or two adenomas possessing no advanced features are classified as "low risk". At the opposite end of the spectrum, it is agreed that finding high grade dysplasia or greater than 10 adenomas confers a "high risk".

Current guidelines' variability in recommendations is due to the lack of good quality evidence to support surveillance strategy.

UK guidelines do not take account of polyp architecture, while guidance in the USA and Europe classifies individuals with a villous adenoma as "high risk". In a comparison of current UK and US guidelines, it was found that following UK guidelines would better identify a group of patients at high risk of advanced neoplasia: those with ≥5 small adenomas or ≥3 adenomas including at least one of ≥10mm. These patients would be offered a surveillance interval of 3 years according to US guidelines or 1 year according to UK guidance. At one year follow-up, this group had an 18.6% risk of advanced neoplasia[64].

Conversely, patients with 1 or 2 small adenomas would be classified as low risk by UK guidelines regardless of histology. This group could be at relatively high risk if histology revealed advanced adenomas (HGD or villous architecture) and as such would be advised 3 year surveillance under US guidelines. The same group of patients could have been offered no surveillance by following UK guidelines, but have a 7.1% absolute risk of advanced neoplasia at 1 year[64].

Current guidelines take account of findings at both the index and first surveillance colonoscopy in determining the second surveillance interval. This approach would be supported by a recent study showing that high risk features identified at either the index or first surveillance procedure increase the risk of advanced neoplasia at second surveillance[65].

More recently, the criteria for risk stratification has been challenged by a retrospective study of post-polypectomy surveillance in the UK in the intermediate risk group. A key finding of the Intermediate Adenoma trial[66] was the identification of two subgroups based on the presence of at least one of four risk factors. In the intermediate risk group studied, those with none of these risk factors: a suboptimal quality colonoscopy, proximal polyps, or a high-grade or large adenoma (≥20 mm) at baseline, had a lower CRC incidence than in the general population (SIR 0·51, 95% CI 0·29–0·84) *without* any surveillance. Therefore the risk reduction can be attributed to the effect of the baseline colonoscopy and polypectomy.

Surveillance Intervals

High risk

The evidence to support the use of surveillance applies predominantly to the "high risk" group. The incidence of advanced neoplasia and carcinoma in these individuals is significantly increased at follow-up, and CRC mortality is reduced by their surveillance[34,59,60].

Data from the UK screening programme shows that in high risk individuals (by UK guidelines), the overall yield for advanced neoplasia at first surveillance (at 12 months) was 6.6%, with a yield of 0.8% for CRC. These findings would support the current strategy of 12 month surveillance in this group[67]. The same study found that villous architecture and a right-sided

adenoma at the index procedure were associated with an increased risk of finding advanced neoplasia at 1 year follow-up. Therefore within the high risk group, there are other factors which could be used to further inform the appropriate surveillance interval for an individual.

Current US guidelines classify patients with >10 adenomas as highest risk. However, as only 0.1% of screening patients fall into this category, its clinical utility is limited.

Low risk

Within the low risk group, it is known that the absolute risk of advanced neoplasia at follow-up is low. Current guidelines are based on evidence that this group carries no increased risk of CRC compared to the general population[24,26]. A recent meta-analysis suggested individuals in the low risk group at the index procedure have a higher risk of advanced neoplasia at follow-up compared to those found to have no adenoma[68]. However, the absolute risk in both groups remains very low.

On the basis that the low risk group carry a risk of CRC equivalent to the general population, the guidelines advise surveillance at the interval prescribed by the relevant screening programme, i.e. effectively advising no increased surveillance over that of the general population. The UK guidelines

allow for deviation from this rule in that the low risk group may be offered no surveillance or a further procedure at 5 years. Of note, the English Bowel Cancer Screening Programme (BCSP), while following UK guidelines (BSG, 2010 and NICE, 2011), offers no surveillance in this group.

Recent data from Norway suggest a significant reduction in CRC mortality at 7.7 years in "low risk" patients after a single screening examination[69]. However, the definition of "low risk" used in this study differs from that used in current guidelines as the study authors used cancer registry data and so did not have access to details of polyp size or number. Therefore, all patients with "multiple" polyps or with histology showing either villous architecture or high-grade dysplasia were classified as "high-risk". This definition makes comparison with other studies difficult.

Intermediate risk

Current guidelines differ most in recommendations for individuals with intermediate risk. It is in this group of patients that the benefit of surveillance is most uncertain.

Patients with 3 or 4 diminutive adenomas at index colonoscopy would be offered a surveillance procedure at 3 years according to UK, European, and US guidelines. However, there is little evidence that this group of patients carries any significantly increased CRC risk compared to the general population.

There is evidence for the increased risk of identifying further adenomas at first surveillance in patients classified as intermediate risk at index procedure. However, the relative risk varies within this group of individuals dependent upon factors such as polyp size, patient age, and the presence of advanced adenoma at the index procedure, i.e. with the varying definition of intermediate risk [70]. Evidence for an effect of surveillance on CRC incidence and mortality is lacking.

Serrated Lesions

American and European guidelines include serrated polyps in their recommendations, which are not specifically dealt with in UK guidelines.

Serrated polyps are known to be more challenging to identify at colonoscopy and their predilection for the proximal colon is thought in part to explain the relatively lower protective effect of colonoscopy on incidence of right-sided CRCs [11].

Significant variability in detection of these lesions by endoscopists and their classification by pathologists has caused evidence on their natural history and risk profile to be lacking. However, further study and increased awareness of

these lesions is likely to lead to further recommendations for surveillance in individuals found to have serrated polyps.

Disadvantages and limitations of surveillance

At present, surveillance procedures account for 20-30% of capacity in endoscopy departments: approximately the same proportion as primary screening procedures[71-74]. It is likely that demand for surveillance procedures will increase in line with more widespread implementation of screening programmes, rising adenoma detection rates associated with modern endoscopes and rising quality standards, and the increased recognition and surveillance of serrated lesions.

While colonoscopy is a generally safe procedure, there is a risk of major complications[75]. As such, the decision to proceed with surveillance colonoscopy must be informed by both the risk of CRC and the risk of a complication related to the procedure. Additionally, even an uncomplicated colonoscopy may represent considerable burden on the patient, who undergoes bowel preparation, time off work, and potential discomfort during the procedure. Fear of pain during the procedure is known to reduce the uptake of screening colonoscopy[76,77]. For surveillance programmes to be effective, uptake must be maximised. By definition, individuals invited for surveillance already have personal experience of colonoscopy. This experience

is likely to inform the individual's decision on whether to undergo a surveillance procedure, highlighting the importance of patient experience during colonoscopy.

When to stop surveillance

The decision to discontinue surveillance is guided in current literature only on the criterion of the patient's chronological age[78]. It is known that rates of complications and post-procedure hospital admission are increased with advancing age and multi-morbidity. Advancing age also reduces the potential survival benefit in surveillance: as progression from adenoma to carcinoma is likely to take around 10 years, patients with a life expectancy of a similar or shorter time have little chance of benefit from a surveillance colonoscopy.

However, the use of chronological age alone is an over-simplification of the decision to discontinue surveillance: a decision which must balance the relative risks for the individual.

Patients found at their initial procedure to have an advanced adenoma, have a CRC risk similar to that of the general population after just one surveillance follow-up colonoscopy[24,59]. Further study is needed to identify more detailed criteria to guide the decision on continued surveillance.

Adherence

There is strong evidence that adherence to current guidelines by physicians is highly variable[79]. Some surveillance procedures are performed earlier than advised, some late, and some not performed at all. Clinical guidelines are only a guide to clinicians and many will choose to advise a different approach for an individual patient.

Also, patients may choose not to be subjected to surveillance procedures for multiple reasons including their experience of colonoscopy and the perceived benefits of surveillance. The subject of patient choice in surveillance is an area requiring further study.

Further study

Progression from adenoma to cancer usually occurs over many years. As such, the benefits of surveillance of colonic adenomas in reducing morbidity and mortality can only be realised over the long term. The introduction of surveillance programmes has become widespread only in recent years, so far limiting the available data on long-term follow-up. The known increased risk of CRC in patients found to have adenomas would make a randomised trial comparing surveillance to no surveillance unethical. Therefore, further study

of the data from the era of widespread adenoma surveillance is needed to better inform future practice.

Current guidelines base recommendations on data collected prior to the widespread implementation of population screening programmes and prior to the use of robust quality metrics in colonoscopy. These factors may significantly alter the population classified within each risk group and so have a major impact on the outcomes of each group. More contemporary data from the era of high quality colonoscopy and population screening may allow more accurate risk stratification to better utilise limited colonoscopy resources in the future.

The future of adenoma surveillance

Polyp factors may be used, as in current guidelines, to determine surveillance interval. However, including other patient factors in this assessment may allow more accurate risk stratification. Possible factors include age, sex, family history of colorectal cancer, smoking status, or obesity.

Additionally, this combination of polyp and patient factors may further inform the decision on whether to continue with any further surveillance after the first surveillance procedure, as it is the first surveillance procedure that has greatest effect in reducing the future risk in the highest risk patients.

Summary

Internationally, increasing numbers of patients are embarking upon a course of surveillance colonoscopies due to the polyps discovered at the time of a previous examination. Each colonoscopy involves the burden of bowel preparation, potential anxiety and discomfort, and risk of complication for the patient. In many health settings, colonoscopy is a finite resource and so must be recommended only with a strong indication.

It is believed that individuals with non-advanced adenomas have no significantly increased risk of colorectal cancer compared to the general population. In addition, patients found at their initial procedure to have an advanced adenoma, have a CRC risk similar to that of the general population after just one surveillance follow-up colonoscopy[24,59].

As discussed previously, there is some retrospective evidence to support surveillance procedures in patients at the highest risk of CRC. For those at lower risk, further evidence is needed to better stratify risk and so inform discussions between the individual and their clinician on whether surveillance colonoscopy is appropriate.

CHAPTER 3 – Systematic review

The purpose of this review was to determine advanced adenoma and colorectal cancer incidence in patients who have undergone post-polypectomy surveillance colonoscopy for intermediate risk colorectal adenomas.

It is widely accepted that the majority of colorectal cancers develop via the adenoma-carcinoma sequence. As such, the intermediate adenomatous stage presents an opportunity to arrest progression along this path to cancer development. Colonoscopy and polypectomy significantly reduces CRC incidence. What is less clear, however, is the benefit of further surveillance colonoscopy after initial polypectomy.

Post-polypectomy surveillance is now a common indication for colonoscopy and is supported by clinical guidelines in the UK, Europe, and the USA. However, evidence to support current post-polypectomy surveillance practice is lacking. Prolonging the interval between surveillance colonoscopies would reduce the burden on patients (of potential discomfort and complications) and on limited colonoscopy resources, thereby reducing waiting times and so minimising delayed diagnosis.

The decision on whether to advise surveillance and at what interval is informed by the findings of the index colonoscopy. Clinical guidelines stratify

findings as “high” or “low” risk, with the UK guidelines also including an “intermediate” category.

A recent survey of leading researchers in the field of gastrointestinal endoscopy identified surveillance strategy as the single most important research priority across all disciplines in GI endoscopy[80].

The timing of surveillance colonoscopy may be considered on the basis of the yield of pathology at surveillance. In simple terms, the finding of CRC at surveillance implies that the interval has been too long. However, diagnosis of cancer at surveillance colonoscopy cannot be expected to drop to zero even with very frequent surveillance. This is because a proportion of cancers detected at surveillance arise from missed lesions which were present at the time of previous colonoscopy. Very frequent surveillance may minimise the rate of CRC detected, but at the cost of additional unnecessary colonoscopies. Adenomas are commonly classified as advanced or non-advanced, with advanced features being any one of: diameter ≥10mm, villous architecture of >25%, or high-grade dysplasia. Arguably, the detection of non-advanced adenomas at surveillance is of lesser importance due to the natural history of colorectal adenomas. It is believed that progression from non-advanced adenoma to carcinoma occurs over a period of 5-20 years. Of greater significance, a finding of advanced adenoma at surveillance provides the

opportunity for further polypectomy and arrest of the adenoma-carcinoma sequence.

Optimal use of surveillance colonoscopy, therefore, would maximise advanced adenoma incidence without increasing cancer incidence. In order to address these criteria directly, this systematic review sought to determine the yield of advanced adenoma and cancer at post-polypectomy surveillance.

Data from the English Bowel Cancer Screening Programme (BCSP) has shown that in a UK population aged 60-69 years, faecal occult blood test (FOBt) positivity ascribes a high rate of neoplasia at initial screening colonoscopy:

Results from the first two years of the screening programme showed 17,518 screening colonoscopies performed, yielding 1772 (10.1%) cancers, 3050 (17.4%) with intermediate risk findings, and 1721 (9.8%) with high risk findings. In total, this represents 37.4% with advanced neoplasia (finding of CRC and AA combined)[81].

BCSP data has also shown a high yield of advanced neoplasia at first surveillance colonoscopy at twelve months after baseline in the "high risk" group[82]. It should be noted that further colonoscopy at such a short interval after the index procedure may be considered a "clearing" colonoscopy rather than true surveillance. This is because the additional polyps detected twelve

months after the index procedure are most likely to have been present at the time of the index procedure: that is, they are missed lesions.

At the opposite end of the risk spectrum, "low risk" findings at baseline do not confer an increased risk of colorectal cancer compared to those with no adenoma. For this reason, clinical guidelines in the UK suggest either no surveillance or surveillance at a five year interval. In the case of the BCSP, no surveillance is performed in this group.

Therefore, this review focused on those individuals in whom there are intermediate findings at baseline. This group falls into the UK "intermediate risk" category and in US guidelines would be described as "higher risk". Suggested practice is for this group to be offered surveillance at three years. However, a number of papers have advised that extension of this interval to five years would not significantly increase the incidence of CRC.

In order to evaluate the evidence for this proposal, this study systematically reviewed the published literature on AA and CRC incidence in this intermediate risk group.

Methods

Search strategy

Two electronic databases were searched: Embase 1996 to 2016 and Ovid MEDLINE In-Process & Other Non-Indexed Citations. The search strategy was as follows:

1. polyps/

2. intestinal polyps/

3. colonic polyps/

4. exp adenomatous polyps/

5. (polyp? or adenoma$).tw.

6. or/1-5

7. exp colonoscopy/

8. (colonoscop$ or coloscop$ or sigmoidoscop$ or chromoscop$).tw.

9. or/7-8

10. population surveillance/

11. follow-up studies/

12. or/10-11

13. 6 and 9 and 12

14. remove duplicates from 13

15. limit 14 to "all adult (19 plus years)"

16. limit 15 to english language

17. limit 16 to humans

18. limit 17 to (article or book or book series or chapter or editorial or erratum or journal or note or report or "review" or short survey or trade journal or addresses or autobiography or bibliography or biography or case reports or classical article or clinical conference or clinical study or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comment or comparative study or congresses or consensus development conference or consensus development conference, nih or controlled clinical trial or "corrected and republished article" or dataset or dictionary or directory or duplicate publication or english abstract or evaluation studies or festschrift or government publications or guideline or historical article or in vitro or interactive tutorial or interview or introductory journal article or journal article or lectures or legal cases or legislation or meta analysis or multicenter study or news or newspaper article or observational study or overall or patient education handout or periodical index or personal narratives or portraits or practice guideline or pragmatic clinical trial or published erratum or randomized controlled trial or "research support, american recovery and reinvestment act" or research support, nih, extramural or research support, nih, intramural or research support, non us gov't or research support, us gov't, non phs or research support, us gov't, phs or retracted publication or "retraction of publication" or "scientific integrity

review" or systematic reviews or technical report or twin study or validation studies or video-audio media)

19. limit 18 to yr="2000 -Current"

Publication year excluded papers prior to 2000. Major advances in colonoscopy quality have been achieved in recent years: rates of caecal intubation and adenoma detection are considerably higher than in the 1990s. As fewer adenomas are missed, and more adenomas are removed, the true future risk of advanced adenoma and cancer is reduced. However, the appreciation of more adenomas increases the risk category assigned and so increases the use of surveillance. It is therefore essential that the evidence reviewed is contemporary. On the other hand, a sufficient duration of follow-up is required to reflect the risk of advanced neoplasia during follow-up. The year 2000 was chosen to balance these conflicting requirements for sufficient follow-up while limiting evidence to the modern era of high quality colonoscopy.

Selection criteria

Titles and abstracts of each paper in the search results were individually evaluated according to the following inclusion criteria: (1) full article publication, (2) publication year 2000-2016, (3) study design: randomised control trial (RCT) (chemoprevention trials were included if no significant difference was found between the intervention and control group or if results from the placebo group were reported separately), cohort study, case control

study, database analysis, (4) study population: adults (age ≥18 years) with a personal history of colorectal adenoma(s), (5) intervention: repeat colonoscopy (surveillance or other indication), (6) results: incidence of recurrent advanced adenoma or colorectal cancer.

Exclusion criteria were (1) studies including patients with a personal history of colorectal cancer, familial adenomatous polyposis (FAP), hereditary nonpolyposis colorectal cancer (HNPCC), or inflammatory bowel disease (IBD).

Potentially eligible papers were further reviewed in full text format against the above criteria.

Data extraction and analysis

Data were extracted from included papers and entered into a spreadsheet using Microsoft Excel® (Microsoft Corporation, Redmond, WA). The data extracted consisted of (1) patient demographics, (2) year of baseline colonoscopy, (3) baseline colonoscopy findings (risk classification and/or presence of advanced adenoma), (4) surveillance interval, (5) geographic location of the study population, (6) setting (screening programme, symptomatic, or mixed), (7) findings at surveillance (AA and/or CRC), (8) total CRC incidence during follow-up.

The included papers were reviewed by a second reviewer, Dr Ravi Ranjan, gastroenterology specialty registrar in the Northern Deanery. Any papers where there was a difference of opinion on inclusion, were resolved by consensus. The results extracted from the paper were also reviewed by Dr Ranjan and any disparities resolved by consensus.

PRISMA diagram

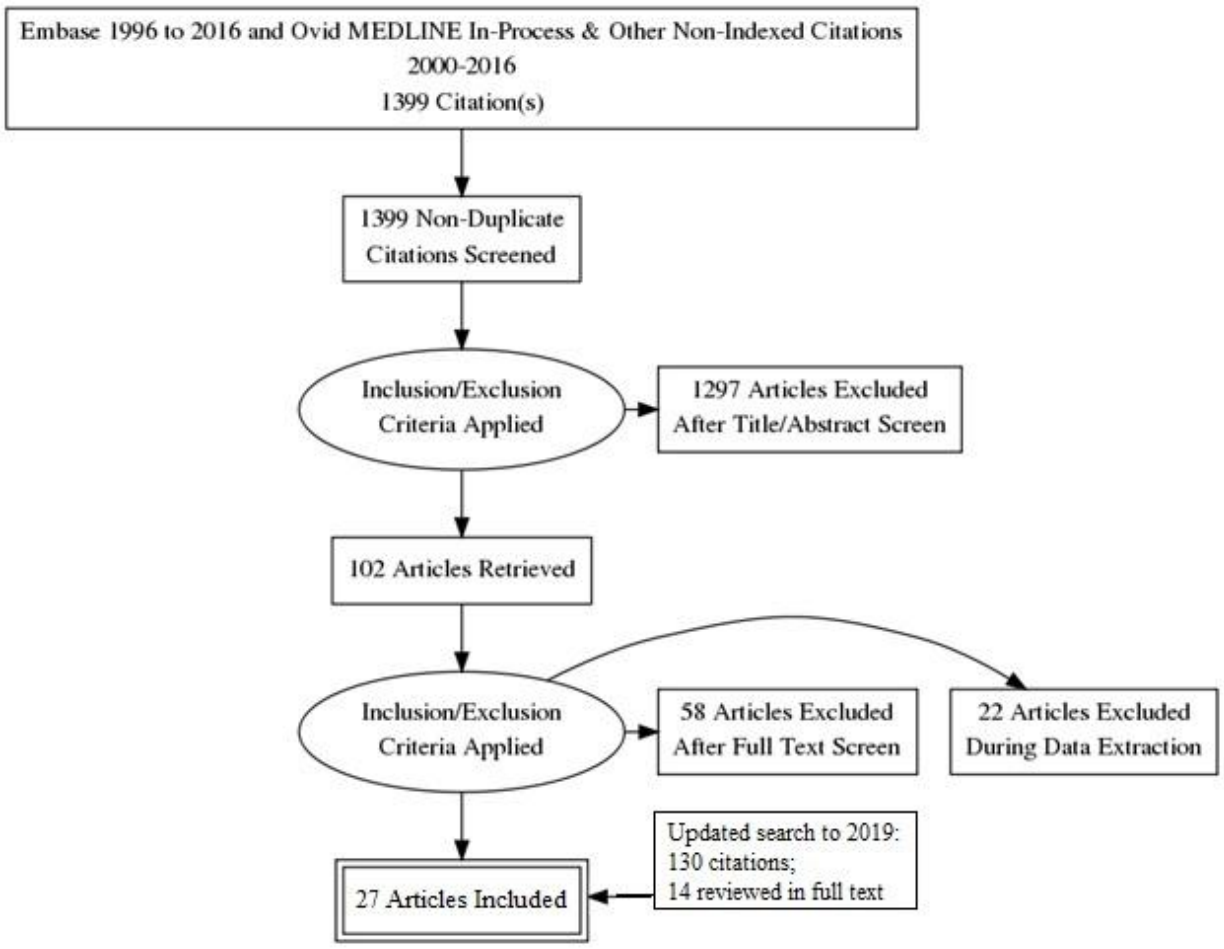

Figure 1 PRISMA diagram

Results

Characteristics of the selected studies

The initial search yielded 1399 unique results when run on 25th August 2016. After review, a total of 22 papers were included for final analysis. The above PRISMA diagram shows the outcome at each stage of the selection process.

The 22 included papers reported results from a total of 20 different studies.

The literature search was repeated on 18th September 2019 in order to update the findings of this review. The "Search strategy" above was used with the date range amended to "2016 – Current". This returned a total of 130 results. After title and abstract review, 14 of these papers were reviewed in full text. Five papers[66,83-86] were ultimately included after full text review and data extraction, bringing the total number of included articles to 27.

The studies varied in design, population, and reported outcomes. Eighteen studies were retrospective analyses of a database[66,83-99]. There were four randomised control trials (RCTs) of treatments being investigated for chemo-preventative effects[100-103] on the development of adenomas. One case control study[104], one prospective cohort study[105], and one randomised trial of screening for the prevention of cancer[106] were also included.

The geographic spread of the study locations covered the USA, Europe, and Korea. Of note, no studies from Japan were included due to the differing histopathological assessment of colorectal adenomas in Japan compared to the USA and Western Europe. In order to assess both the initial risk category and the nature of recurrent neoplasia, there must be standardisation of the definitions for grade of dysplasia and cancer. It has been shown that pathologists from Western countries and Japan presented with the same colorectal histology slides did not concur on diagnosis[107]. For eleven slides that showed adenoma according to Western pathologists (with low grade dysplasia according to at least half of them), Japanese pathologists diagnosed definite carcinoma in four cases and adenoma in five. In the remaining two cases, they were equally divided between a diagnosis of adenoma and carcinoma.

The included studies comprised twelve from the USA, eight from Western Europe, and five studies from South Korea.

Risk of CRC at surveillance based on baseline findings

Fourteen studies[66,83-87,89-92,96,98,102,108] reported rates of CRC detected during surveillance. However, in ten of these, only CRC detected at a surveillance procedure was reported. Therefore, in all but four studies[66,84,87,108], diagnoses of CRC during the study follow-up period, have only been captured by the study if diagnosed by surveillance colonoscopy.

Table 1 CRC incidence

Study	Reports total CRC incidence (including diagnosis outside surveillance)	Duration of follow-up (Y)	N	CRC incidence (%)
Atkin, 2017	Y	7.9	11944	1.75% overall, including those with no surveillance
Cottet, 2012	Y	7.7	5779	1.5% overall, including those with no surveillance
Cubiella, 2016	Y	3.1	5401	0.4%
Mouchli, 2018	N	2.3	3406	3.1%
Ren, 2016	N	3-5	2478	0.5% HR
Leung, 2010	Y	4.3 – 10.5	2079	1.1%
Jung, 2016	N	4	1646	0
van Heijningen, 2015	N	Appropriately timed	602	0.4%
Robertson, 2009	N	6	564	0.2% HR
Pérez-Cuadrado-Robles, 2016	N	Unknown	561	0.4%
Kwah, 2014	N	4	449	0
Lee, 2015	N	4	433	0.5%
Lieberman, 2007	N	5.5	376	0.8% if ≥3 small adenomas; 0.8% if large TA; 1.2% if villous; 4.4% if HGD
Baik, 2017	N	3.4	350	0.6%

An even greater limitation of the reporting of CRC rates is the time period over which the adenoma-carcinoma sequence is thought to progress. CRC rates at 5 years are likely to represent missed lesions or incomplete resection of adenomatous tissue. In view of the timescale over which non-advanced adenomas progress to cancer, the effect of polypectomy on cancer incidence would be expected to be realised at 10-15 years later.

However, for results to represent true clinical scenarios, it is the overall rate of CRC that is relevant. Many papers have attempted to classify cancer according to their likely origin. For example, cancers diagnosed within three years of a colonoscopy are, by convention, termed interval colorectal cancers (ICC). This is due to the acceptance that a cancer will not develop from normal colonic tissue over such a short time period. Within the definition of ICC, further classification can be attempted by correlating the findings of the previous colonoscopy with the site of the cancer. If the cancer has developed in the same colonic segment as a previous polypectomy, this can be attributed to incomplete resection of adenomatous tissue. On the other hand, a cancer detected in a colonic segment previously reported to be clear of adenomas, can be termed a "missed lesion".

Review of the above tabulated results reveals the higher incidence of cancer in cases where baseline adenomas displayed villous histology or high grade dysplasia. Overall, there does not appear to be a significant difference in cancer

rates between the “low” and “high” risk groups. This must be interpreted with the caveat that the duration of follow-up is short.

Risk of advanced adenoma at surveillance based on baseline findings

Table 2 AA incidence

Study	Baseline risk group	Duration of follow-up (Y)	n	Cumulative AA incidence (%)
Cubiella, 2016	EU IR/HR	3	3536	13.8
Stock, 2013	US HR	3	1584	14.2
Pinsky, 2009	AA	3	1057	10.5
van Heijningen, 2015	US HR	3	602	4.0
Bonithon-Kopp, 2004	2 adenomas or 1 >5mm	3	468	6.2
Lee, 2015	US HR	3	433	9.1 (if 1 HR finding) 11.0 (if 2 HR findings) 18.9 (if 3-4 HR findings)
Morelli, 2013	AA	3	349	12.9
Kwah, 2014	US HR	3	185	16.8
Baik, 2017	US HR	3	179	10.2
Jung, 2016	AA	4	1646	15.7
Laiyemo, 2009	US HR	4	389	8.7
Chung, 2011	US HR	5	539	12.2
Lieberman, 2007	US HR	5	376	11.9 (if ≥3 small NAA) 15.5 (if large TA) 16.1 (if villous) 17.4 (if HGD)
Miller, 2010	AA	5	44	26.1
Pérez-Cuadrado-Robles, 2016	EU IR	Unknown	561	7.3

US HR = United States "high risk" category. AA = advanced adenoma. NAA = non-advanced adenoma. TA = tubular adenoma. HGD = high grade dysplasia.

Fifteen studies report AA rate at surveillance. As is the case with diagnosis of CRC at surveillance, it must be recognised that an advanced adenoma detected at a surveillance colonoscopy may represent a lesion missed at previous colonoscopy, particularly as the miss rate for small and diminutive adenomas is higher than that for lesions ≥10mm in diameter. Depending on the interval since last colonoscopy, it is also possible that an advanced adenoma may arise from colonic tissue which appeared normal at the time of previous colonoscopy.

The results presented in the above table show a range of AA recurrence rates at 3, 4 and 5 years of 4.0-18.9%, 8.7-15.7%, and 11.9-26.1% respectively. At five years, the highest reported AA rate was 26.1% in a study including only 44 patients with AA at baseline. Other studies reported rates up to a maximum of 17.4%.

Discussion

The key finding of this systematic review was that the rate of advanced colonic neoplasia at surveillance did not differ significantly at a three or five year interval after intermediate risk findings at baseline. This finding may have considerable implications for clinical practice. As detailed in the introduction to this review, many thousands of individuals across the globe undergo colonoscopy as a surveillance procedure after the finding of adenomas and intermediate risk categorisation. Current clinical guidelines in the UK, Europe and USA suggest that the interval before surveillance in this group should be three years. Furthermore, it is recognised that clinical practice often deviates from the clinical guidelines and that in many cases, surveillance is performed *earlier* than guidelines would advise. The findings of this review suggest that deferring surveillance to five years after baseline colonoscopy in the intermediate risk group would not significantly increase the detection of colorectal cancer or of advanced adenomas.

The strengths of this study are the systematic selection of studies for inclusion focusing on the key clinical question of appropriate surveillance for the intermediate risk group. The large number of patients included adds weight to the findings. The results of these studies are highly relevant to a Western population, with the vast majority of patients located in the USA and Europe in the setting of standard endoscopy and histopathology practices in the West.

Similarly, studies performed before the era of modern endoscopic techniques were excluded. This is of particular importance in ensuring relevance to current clinical practice. The quality of colonoscopic examination is variable[54,109,110], but has increased significantly since the advent of flexible colonoscopy in 1969. Fibre optic scopes with an eyepiece were superseded in the 1980s by video chip technology allowing transmission to a video screen.

Modern day colonoscopists are acutely aware of the quality standards expected of them and a number of factors are routinely audited: particularly caecal intubation rate (CIR) and adenoma detection rate (ADR). This focus on measuring quality is, however, a relatively recent development. In the UK, the Joint Advisory Group on GI Endoscopy (JAG) oversees training and quality and was established in 1994. In 2006, two landmark events secured the current era of quality assurance in colonoscopy. In the USA, a taskforce of the American Society of Gastrointestinal Endoscopy (ASGE) and American College of Gastroenterology (ACG) published "Quality Indicators for Colonoscopy". During the same year, the UK Bowel Cancer Screening Programme (BCSP) commenced.

The quality of colonoscopy has a fundamental impact on post-polypectomy surveillance. An endoscopist or programme with a lower ADR is more likely to miss adenomas. Missed adenomas have two compounding effects. Firstly, adenomas can only be resected if they are detected, and so the adenomas not

detected remain in situ and may progress in size and histology further along the adenoma-carcinoma sequence. Interval colorectal cancer (ICC) is higher in patients whose baseline colonoscopy was performed by an endoscopist with a lower ADR[3]. As well as remaining in situ and increasing the risk of advanced colorectal neoplasia, missed adenomas are not counted and not taken into account in assigning a risk category to inform a decision on surveillance interval. Therefore, while the patient is at an increased risk of advanced neoplasia due to a higher rate of missed adenomas, they are also classified as lower risk and advised to have a longer interval before surveillance colonoscopy. Conversely, a high-ADR colonoscopist is less likely to miss adenomas and will therefore resect a higher number of adenomas. This has the effect of both reducing the true risk of advanced neoplasia whilst also increasing the risk group to which the patient is assigned and so reducing the surveillance interval. It should be noted that the concept of paradoxical over-surveillance in the patients of high-ADR colonoscopists has been questioned.

While there are significant strengths in focussing on studies performed in recent years, this does impose a significant limitation in the correspondingly short duration of follow-up. The ultimate success in the detection and resection of colorectal adenomas is in reducing the incidence and mortality of colorectal cancer. Due to the protracted time of progression along the adenoma-carcinoma sequence, this effect of can be measured directly only after at least ten years of follow-up.

It is believed that a small minority of colorectal cancers may develop de novo from macroscopically normal colonic mucosa rather than following the traditional adenoma-carcinoma sequence. These lesions may account for a proportion of those cancers occurring within three to five years of a colonoscopy. However, the majority of these cancers represent missed lesions; that is missed cancers or missed adenomas that subsequently progress to cancer. For this reason, frequent colonoscopy is not a substitute for high quality colonoscopy.

The traditional adenoma-carcinoma sequence is one of three described mechanisms of carcinoma development and is thought to account for the largest proportion (50-70%) of CRCs in a Western population. The serrated pathway accounts for 10-20% of cancers. Serrated lesions are increasingly recognised by endoscopists and pathologists and are thought to account for the reduced effectiveness of colonoscopy in prevention of CRC in the proximal colon compared to the distal colon. The third pathway is more heterogeneous and described as the alternative pathway. This pathway may account for 10-30% of cancers and may progress through serrated or villous stages[111].

In this review, studies including colonoscopies performed prior to 1990 were excluded. A separate analysis was also performed excluding studies in which colonoscopies were performed prior to 2000. Most of the included studies have a median follow-up duration of less than five years. As such, it may be argued

that the sub-analysis of studies performed solely since 2000 is more reflective of present day clinical practice whilst reporting on findings over a similar follow-up duration.

Clearing colonoscopy

More polyps are missed during a colonoscopy which detects multiple polyps. This knowledge has led to the proposal that a second colonoscopy at a short interval of up to twelve months be considered primarily as a "clearing" colonoscopy. This term acknowledges that any lesions detected and resected at this short interval represent missed lesions which were present at the time of the previous examination. It is unlikely that a new adenoma would develop or an existing adenoma progress significantly in over a time interval of less than twelve months.

One study in this review reports only on findings at first surveillance colonoscopy performed at an interval of twelve months from baseline. While the term "surveillance" is used in this study, it may be considered more accurate to refer to these repeat examinations as "clearing" colonoscopies. As such, this study has not been included in the full analysis.

Another large study: the Polyp Prevention Trial (PPT), performed a second colonoscopy at twelve months after baseline and included the findings at this

procedure as part of the "baseline" findings. This approach differs from other studies and so limits comparability of the findings. It is, however, an approach which may represent the appropriate approach to surveillance practice.

In total, four included studies[95,102,106,112] report findings of second surveillance (that is, the third colonoscopy) and aim to define predictive factors from the previous two colonoscopies. This study design is based on the understanding that a second colonoscopy after adenomas are found at baseline represents a second opportunity to detect and resect remaining adenomas. If the second procedure is considered a clearing procedure, and so part of the "baseline", then subsequent surveillance must be based on a summation of the findings at both first and second colonoscopies.

Studies show that having had findings classified as "high risk" at a previous colonoscopy may still confer increased risk of advanced neoplasia, even if the second colonoscopy itself detects "low risk" or even no adenomas.

Limitations of this review

There was a high level of heterogeneity between the included studies. The baseline groups included for analysis were generally similar in demographics:

Western populations in the 50 to 80 years age range with a preponderance of male subjects.

The adenoma characteristics at baseline differed. This was partly due to the differing definitions of intermediate risk. Indeed, the terms used differ such that UK "intermediate risk" is similar to US "high risk". Many studies classify baseline risk on the presence or absence of AA at baseline. For the purposes of the full analysis, these groups have been considered similar. Interestingly, when assessing results for each of these groups individually, it is seen that AA recurrence rates do prove to be comparable.

It was a limitation of the majority of included studies, and by extension of this review, that colonoscopy quality measures are generally not reported. As discussed above, the decision to limit this review to studies published since 2000 and to exclude studies with colonoscopies performed prior to 1990, was based on the improved quality of colonoscopy in the modern era. There is, however, a paucity of specific quality indicators reported in the included studies. Quality of bowel preparation, caecal intubation rate (CIR), and skill of the colonoscopist are factors known to affect adenoma detection. Adenoma detection is fundamental to the initial risk categorisation of the study subject as well as to their true risk of future advanced neoplasia. Year of colonoscopy has therefore effectively been used as a surrogate marker of higher quality colonoscopy while recognising this as a limitation of the present study.

CHAPTER 4 – Data analysis methods

Aim

The aim of the analysis was to ascertain the benefit of post-polypectomy surveillance within the BCSP. This was done by assessing data from the BCSP database (BCSS) (on individuals who had adenomas removed through screening) and the National Cancer Registration and Analysis Service (NCRAS)(on CRCs detected).

Objectives

1. To determine the adenoma, advanced adenoma and CRC yield at initial surveillance of each colonoscopy surveillance cohort within the BCSP.
2. To determine the factors (adenoma and subject specific) at screening which can predict the outcome of surveillance.
3. To explore the criteria on which to safely stop post-polypectomy surveillance.

Question	Detail	Rationale	Type
Current situation			
1. What surveillance pathway do people take?	Map out the various pathways/numbers that surveillance individuals take.	Overview of workload and complexities.	Descriptive.
2. What is the yield of colorectal neoplasia at BCSP 1st surveillance? a. 1 year surveillance (HR) b. 3 year surveillance (IR)	Split into CRC, AA, NAA	Understand the yield of 1st surveillance, helps to determine whether this is worthwhile	Descriptive.
Can we do better?			
3. Can we find a better way of stratifying people at baseline?	Clinical and person-related characteristics.	Potentially reduce number commencing surveillance	MVA

4. Can we find a cohort who can safely stop surveillance?	Analyses above will explore this. This is the most challenging aspect (cf. evidence to delay surveillance).	Reduce number entering surveillance or undergoing ongoing surveillance	Descriptive & MVA
5. Can we find particularly high yield cohorts, who should undergo the most intensive surveillance?	Analyses above will explore this. Look for "polyp-producing" cohorts – those producing multiple adenomas (both NAAs and AAs) after baseline polyp clearance.	Focus resource on those who continue to produce polyps and therefore (probably) have greatest future CRC risk.	Descriptive & MVA

Design

This was a retrospective cohort study of a proportion of the population screened in the English Bowel Cancer Screening Programme, utilising prospectively collected cohort data held on the BCSS.

Setting & Data sources

This analysis was performed at North Tees and Hartlepool NHS Foundation Trust and Durham and Newcastle Universities. The initial data extraction, including anonymization, was performed by the Bowel Cancer Screening Programme of Public Health England, based in Sheffield. The data extracted pertained to participants at all Screening Centres across England.

NCRAS data were linked to screening subjects by PHE England staff using the unique subject identifier for this study. Linked NCRAS data were available until 31/12/2014.

Cohort definition

Participants in the national BCSP who had attended at least one diagnostic test as part of a surveillance episode were included in the cohort. The time period covered included all investigations from the commencement of the BCSP in 2006 until initial data extraction on 03/01/2017. All participants were residents

of England aged over 50 years, generally aged 60 - 74. This full cohort was included for the analyses pertaining to adenomas. A restricted cohort attending surveillance before 30/09/2014 was included in the analyses relating to CRC (because of availability of cancer data; see below).

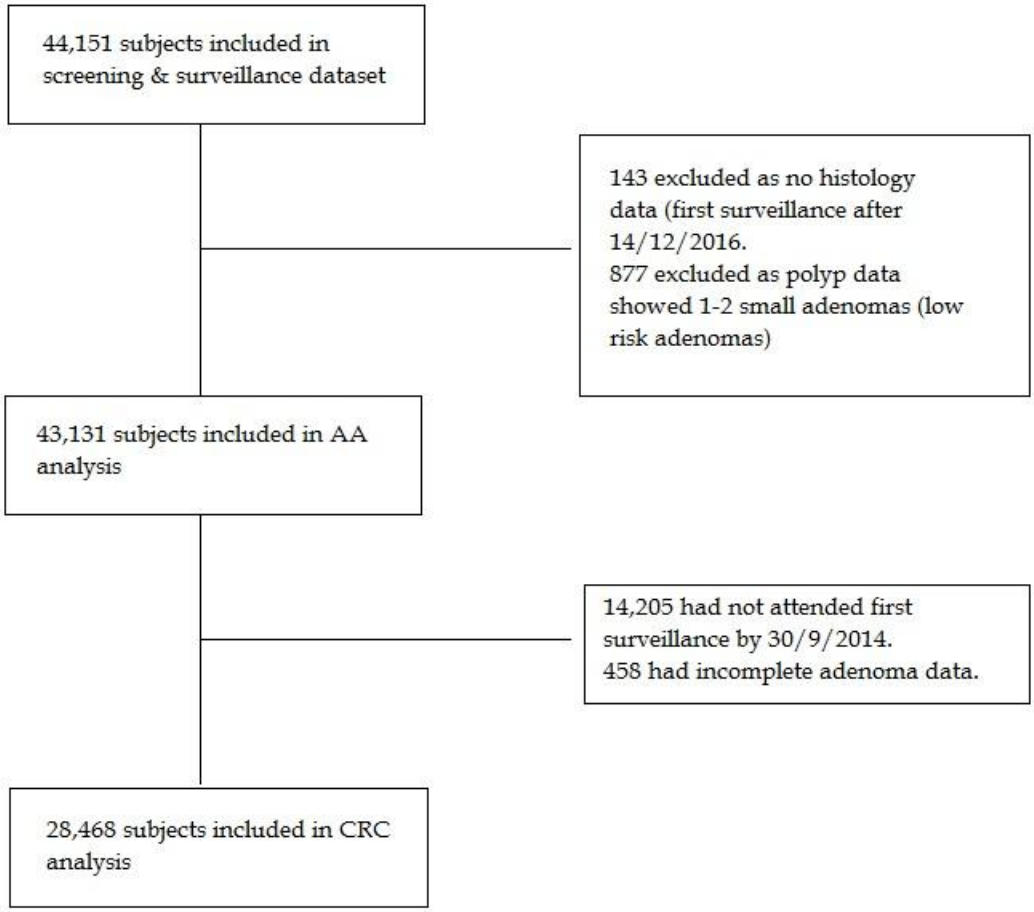

Figure 2 - analysis cohort

BCSS database

The NHS Bowel Cancer Screening Programme (BCSP) in England started in 2006 and had achieved 90% coverage of the population of England by 2009-

2010, for the original 60-69 years age group. Extension of the age category to 74 years began roll-out from early 2010. Individuals registered with a general practitioner are invited to take part using a guaiac faecal occult blood test (gFOBT) starting at age 60. The gFOBT consists of six "windows", each of which may give a positive or negative result for the presence of blood in the stool. A negative gFOBT (all six windows negative) results in a further invitation to repeat the test two years later. If five or six windows are positive, this is immediately classified as a positive result. For test kits showing between one to four windows positive, a second test kit is sent to the individual in order to determine whether further investigation is required. Those ultimately classified as having a positive gFOBT are advised of the need for a secondary screening investigation in order to reach a diagnosis. This investigation will usually be a colonoscopy, but may be a radiological investigation such as CT virtual colonoscopy. All colonoscopies are performed by screening accredited colonoscopists who have undertaken both written and practical assessment. Participating screening centres are approved by the Joint Advisory Group (JAG) on Gastrointestinal Endoscopy.

In March 2013, the English BCSP piloted flexible sigmoidoscopy as a primary screening tool to all persons at age 55. This screening programme has now been adopted as part of the BCSP in addition to gFOBT testing between ages 60 to 74. The roll-out of the Bowelscope programme across England was less than 40% complete by December 2016.

The BCSS is an Oracle® database (Oracle Corporation, Redwood Shores, CA, USA) which was implemented in June 2006 at the inception of the Bowel Cancer Screening Programme. It is a complex relational database containing multiple related tables. Demographic data are held on all screening subjects. Other associated tables hold details of FOBt tests, diagnostic tests, surveillance episodes, and histology data. The database is now held and administered by Public Health England (PHE) as part of PHE Screening.

The NHS Bowel Cancer Screening Programme gathers data on all individuals entering the programme. Further data on individuals undergoing colonoscopy are contemporaneously uploaded by Specialist Screening Practitioners and administrative staff at screening centres around England as the patient passes through the screening pathway. The data are entered via a graphical user interface (known as the Bowel Cancer Screening System-BCSS) onto an Oracle database. Data can be exported to an SQL server to allow specific queries to be written. The benefits of this database are that the data are prospectively gathered and comprehensive. A wide range of parameters are recorded including demographics (age, sex, postcode of address at time of entry into screening programme, relevant medication history, weight and height), faecal occult blood test results, colonoscopy results, histology outcomes and subsequent management.

Access to the national database is restricted. An application, and subsequent amendments, were submitted by the author to the Office for Data Release (ODR) at Public Health England. After approval, a Data Sharing Contract was implemented between PHE and North Tees and Hartlepool NHS Foundation Trust (see Appendix).

National cancer registry data (NCRAS)

Although data on cancers detected within a BCSP episode were including in the original data extract in the Cancer Table, this data was ultimately superseded by the more complete cancer data received in the form of matched, cleaned cancer data originating from NCRAS (the National Cancer Registration and Analysis Service).

NCRAS provided data to the PHE Screening Team on colorectal cancers diagnosed in individuals screened in the BCSP. These data were complete up to 31/12/2014.

NCRAS extracted every bowel cancer where the diagnosis date was between 01/07/2006 (the start of screening programme rollout) and 31/12/2014. NHS Digital matched these tumours to BCSS to identify where an individual had participated in the BCSP. NHS Digital then provided NCRAS the screening details for those individuals.

The following methodology was followed by PHE England staff in order to augment the data held on BCSS with any additional cancer data held by NCRAS. The purpose of this work by the PHE England Screening team was to inform the programme of any cases of colorectal cancer occurring in individuals who had participated in the BCSP. BCSS holds data on cancers detected at a BCSP diagnostic test, but does not include data on cancers detected outside the BCSP (e.g. in the standard symptomatic NHS service).

"For the initial extraction, NCRAS extracted every bowel cancer (cancer occurring in the bowel: diagnosis in the range C18-C21) they had a record of, where the diagnosis date was between 01/07/2006 (the start of screening programme rollout) and 31/12/2014. Date of birth was not used as a matching criterion to ensure that any DOB differences between systems did not inadvertently exclude cases, and to ensure people under the age of 60 who were screened (either due to programme running early or a DOB change) were included.

It is important to note that one person/episode may have greater than one synchronous/primary tumour; in these cases each tumour was extracted.

- These data were then sent to NHS Digital so they could be matched against BCSS – the bowel cancer screening system database.
- NHS Digital checked each NCRAS case to see if that person had ever been invited for, self-referred or opted into bowel cancer screening (gFOBt).

- Where the cases matched, NHS Digital informed NCRAS and provided the screening details for those patients.
- From these data, NCRAS created an algorithm to categorise all the matched screening programme patients/tumours.
- This produced a CSV file of 80,093 bowel cancers (≥ 1 tumour per patient, sometimes across multiple episodes).

Data cleaning

To ensure data accuracy, the following data cleaning protocols were carried out.

NCRAS classification was 'Screen detected' cancer, but BCSS outcome was 'not cancer'

The NCRAS classification rules stated that if a NCRAS registered cancer occurred within a screening programme episode where a diagnostic test took place (or within 3 months of the programme episode closure), then the cancer would be classified as screen detected, even if the screening programme outcome for that episode was not cancer. This was to allow for cancers which were identified at surgery (screening patient referred to surgery) or for patients who, after their initial results, attended a different hospital/private hospital for ongoing care, and histology reports were not accessible/not provided to the screening programme.

150 records were identified where the NCRAS classification stated 'screen detected' but this did not match the BCSS episode outcome. To ensure these cases were correct, each case was reviewed.

In performing this exercise it was identified that within the original extract, NCRAS had included 'in-situ' disease (sometimes called 'behaviour 2') within their initial data extract. It is made clear here that the screening programme does not include in-situ disease, high grade dysplasia, or intramucosal invasion in their definition of cancer.

The outcome of this review flagged 81 of the 150 identified records for removal, specifically:

- 22 cases NCRAS cancelled: in-situ disease only.
- 15 cases NCRAS cancelled: 'referenced off'.
- 9 cases BCSS has proof the case was not cancer –notes from MDM (multi-disciplinary team meeting) / subsequent histology review etc.
- 8 cases screening centre case review determined not cancer.
- 27 cases flagged as not cancer, following interrater review of BCSS episodes, including: investigation datasets, cancer audit datasets, MDM datasets, and subject / episode notes.

N.B. This review had to be carried out where screening centres did not respond to the request to review the case.

It should be noted that 1 case marked for removal, had been classified by NCRAS as 'Interval - Negative Diagnostic Test'. BCSS reported that the episode outcome was in fact 'high risk adenoma'. Interestingly this patient had a screen detected cancer 1 year later. All other cases marked for removal were classified by NCRAS as 'Non-participant FOBt' (1 case) or 'Screen detected' / 'Screen detected extended…' (79 cases).

Important to note:

It is important to note that within the dataset there may be further records identified as cancer, which are in fact in-situ disease, high grade dysplasia, or intramucosal invasion.

This data cleaning exercise can only flag cases for review where BCSS contains a screening programme episode for the same time period where the outcomes from NCRAS and BCSS are different.

BCSS diagnosed cancers not present in NCRAS dataset

Due to the way the initial data extraction was performed: comparing all the NCRAS cancers to BCSS records, a check was performed to ensure there were not any cancers in BCSS that were not in the NCRAS data.

668 patients with 672 tumours (664 patients had 1 tumour, 4 patients had 2 tumours each) were identified as not being present.

Of the 672 tumours identified, 652 had a BCSS result of 'confirmed cancer'.

The further 20 cases had a classification of 'cancer, not confirmed' but each of these cases had one or more of the following:

- a valid Dukes classification
- a TNM values which was not '0' or 'X' (i.e. not T0, N0, M0 or Tx, N0, M0), or blank
- a valid tumour type, (i.e. not 'Not diagnostic of cancer', 'adenoma only' or 'blank').

All 672 cases were deemed to be legitimate cancers in their own right, and so were added into the dataset – classifying each case as either screen or surveillance detected.

Important to note: It is important to note that at this stage of the data cleaning protocol, no checks had been performed to see if any of these added cancers were recurrences.

Cases where episode start date/ end date/ diagnosis dates have been corrected

7 cases had their episode start date, end date and/or diagnosis dates corrected based on BCSS episode data. Scenarios where this occurred are:

- Diagnosis date preceded the start of the screening episode by a matter of a few days, and it could be determined from BCSS records that the cancer was

screen detected, not detected a few days prior to the start of the screening episode.

- The wrong episode had been used to determine the status; there was an episode which more closely matched (or exactly matched) the diagnosis date, than the one used in the classification.

Recurrent cases of cancer

As recurrent cancers are not included in the definition of interval cancers, it was important to identify these cases and flag them for removal from the dataset.

Important to note: This section of the review looks at all patients where the patient had more than 1 episode of cancer.

For this process, the classification of a 'recurrence' was made if:

- a tumour was seen in the same (or very similar[1]) anatomical location at multiple episode (or diagnosis years), and
- the histology description was the same (or very similar[2]).

This meant that 17 recurrence cases were identified and marked as requiring removal, including 3 cases which had been added into the dataset from data cleaning protocol 4.3: BCSS diagnosed cancers not present in NCRAS dataset.

[1] For example: 'Cloacogenic zone' and 'Anal canal', or 'Malignant neoplasm of rectum' and 'Rectum, NOS'

[2] For example: 'Adenoca in adenomatous polyp' and 'Adenocarcinoma in tubulovillous adenoma'

In addition to the above recurrences, 438 patients, which equates to 900 distinct tumours (416 patients with 2 tumours, 20 patients with 3 tumours, and 2 patients with 4 tumours) were flagged as having more than 1 cancer episode which have not been identified as a recurrence.

It is important to note that some of these cases may in fact be recurrences, but insufficiently granular data are available to make this determination, so they have been left as distinct cases.

for example: Patient A: cancer 1: location = 'Colon, NOS' , cancer 2: location = 'Sigmoid'.

Possible Duplicate Tumours

In addition to the recurrence case review, there was also a broader requirement to look at all patients who had more than 1 tumour (>1 distinct tumour ID) in the dataset, irrespective of the episodes where those tumours were reported.

A review of all patients and tumours in the dataset (including the patients/tumours added due to the cleaning protocols), showed 1,614 patients who had more than 1 tumour listed in the dataset, these can be expressed as:

- 1538 patients with 2 tumours in the dataset
- 69 patients with 3 tumours in the dataset
- 7 patients with 4 tumours in the dataset

Of the patients who had more than 1 tumour (1,614 patients, with 3,311 tumours), it was suggested that a portion of these tumours could in fact be the

same tumour seen on more than 1 occasion, for example seen first at diagnosis and then seen again at treatment.

For this process, the classification of a 'possible duplicate' was made if:

- the tumour was seen in the same (or very similar[3]) anatomical location, and
- the histology description was the same (or very similar[4]).

the only exception made to this classification protocol was where the locations of the tumours were 'Anus' and 'Rectum' but the histology of these tumours was reported to be 'Adenocarcinoma' for both or 'Squamous cell carcinoma' for both.

A review of the 1,614 patients (3,311 tumours) found:

- of the 1538 patients who had 2 tumours, 90 patients were flagged as having possible duplicate tumours, this included the 17 cases already flagged as recurrences
- of the 69 patients who had 3 tumours, 6 patients were flagged as having possible duplicate tumours (2 of the 3 tumours were believed to be distinct)
- and of the 7 patients who had 4 tumours, 1 patient was flagged as having possible duplicate tumours (3 of the 4 tumours were believed to be distinct).

[3] For example: 'Cloacogenic zone' and 'Anal canal', or 'Malignant neoplasm of rectum' and 'Rectum, NOS'

[4] For example: 'Adenoca in adenomatous polyp' and 'Adenocarcinoma in tubulovillous adenoma'

Important to note:

It is important to note that currently none of these cases have been marked as cases to be excluded from the dataset, but are flagged so can be excluded if required."

Acknowledgement: Ms C. Nickerson, PHE Screening.

Descriptive methodology

BCSS was interrogated on 3rd January 2017 to include all data from inception of the screening programme to the date of data extraction (2006 – 2017). The data query was written by Claire Nickerson (PHE Screening) in consultation with the author. Due to the structure of the database, including multiple tables, the necessary starting point was to search for subjects who had attended a surveillance episode. All data pertaining to the identified subjects was then extracted from BCSS and transferred to the author in an anonymised form. A unique subject ID was used to identify each subject in this study. No identifiable data (name, address, date of birth, NHS number) were included in the data extraction.

A Data Sharing Contract (DSC) was agreed between PHE Screening and North Tees and Hartlepool NHS Foundation Trust (the Trust). After approval of the

project and DSC with the Trust Research department, the author and the Trust Caldicott Guardian signed the DSC.

The data extraction was electronically transferred using a secure encrypted file transfer facility (NHS sFTP) to the author at North Tees and Hartlepool NHS Foundation Trust. The data was organised in seven Microsoft Excel® spreadsheets (Microsoft Corporation, Redmond, WA, USA) corresponding to the relational tables contained in BCSS. The Excel® files were held securely for the duration of the project on an encrypted drive under the ownership of North Tees and Hartlepool NHS Foundation Trust.

The data provided by the BCSP was abstracted from a relational database with tables for screening episodes, surveillance episodes, diagnostic tests, and polyps. Each individual may have multiple screening episodes, multiple surveillance episodes, multiple diagnostic tests and multiple polyps detected. Moreover, the number of screening episodes, surveillance episodes, etc. varies for each individual. Each of these tables formed a separate dataset. The data fields and possible contents are described in appendix 1.1.

An episode in the BCSP is defined as all investigations and procedures performed from initial screening FOBt to subsequent investigation of a positive FOBt (endoscopic and radiological) and all associated procedures (including polypectomy). This includes short-term follow-up investigations as part of the

same episode of care, such as a repeat endoscopic examination after a large polyp resection ("site check"). Once the colorectum is deemed to be clear of visible neoplasia, an outcome is finalised (e.g. high risk) and that episode is closed in BCSS. If any subsequent surveillance is indicated (for an intermediate or high risk outcome), then this would open a new episode of care: a surveillance episode.

The initial step in the analysis was to turn these tables into a dataset suitable for cohort analysis (i.e. a flat file, bringing together the data from each of the datasets onto with one record (row) per individual). This was essential to enable the "journey" of each individual over time to be examined and analysed. In statistical terms, this enabled person-years-at-risk (follow-up time) to be computed for each individual and appropriate multivariable analysis methods (Cox proportional hazards) for cohort data to be used.

The data processing and analysis was performed in Stata® (Stata Corp, College Station, TX, USA). Stata is particularly well suited to linking datasets and turning "long" datasets (with multiple procedures, for example, per person) into "wide" datasets (where all the procedures for an individual are on one row of the dataset).

Selected data fields were imported to Stata® from each Excel® file. Matching of data relating to each individual was performed using the unique subject ID

created for this project, which was included in every Excel® spreadsheet of the original data extraction.

Follow-up

The cohort was followed over time (retrospectively) to identify surveillance episodes, adenomas (and other polyps as recorded on the BCSS) and CRCs. Surveillance episodes attended before 15/12/2016 were analysed (episodes between 15/12/2016 – 3/1/2017 were excluded due to incomplete pathology data). Linkage to the cancer data recorded by NCRAS, which was undertaken by colleagues at BCSP, identified cancers diagnosed out with the screening programme on or before 31/12/2014. Thus the end of follow-up date for analyses of adenomas/polyps was 14/12/2016 and for the analyses of CRC was 30/9/2014.

Data cleaning

Included in the original data extract were 507 subjects who had entered surveillance within the BCSP via Bowelscope flexible sigmoidoscopy screening and not by gFOBT positivity. This group differed from the primary cohort in a number of important characteristics: their age of initial screening was 55 years (the age at which the Bowelscope programme offers a flexible sigmoidoscopy), and they had qualified for a colonoscopy by means of flexible sigmoidoscopy findings, not gFOBT positivity.

In view of the alternative category of entry to surveillance, it was decided to exclude all subjects screened by Bowelscope from all analyses. Therefore all records (FS Screening and subsequent surveillance) pertaining to these 507 individuals were deleted from the Episode_Table prior to importing data to Stata.

The Episode Table was then split into two separate Excel sheets: one containing all episodes with Episode_Type = Screening (Episode Table_screening) and another containing all episodes with Episode_Type = Surveillance (Episode Table_surv).

Subsequent data cleaning was performed in Stata. First, Episode Table_screening was imported to create a flat file with one row per subject. Screening episodes with an Episode_Result which was not High-Risk or Int-Risk were deleted. It should be noted that for 22 of these deleted records, Episode_Result was "Cancer". On review, the majority of these episodes were thought likely to include the finding of a polyp cancer or cancer type other than colorectal adenocarcinoma (e.g. lymphoma or carcinoid).

This left 44151 rows in the flat Stata file, each with a unique Subject_ID and containing episode data for the initial screening episode with a result of High-Risk or Int-Risk. This file formed the base to which further data were added.

From the original Episode Table data fields imported, Episode_Status, Prevalent_Incident, and Episode_Seq_No were dropped, to leave the following fields remaining:

- Subject_ID
- Episode_ID
- Age_Epi_Start
- Episode_Type
- Episode_Result

Personal details of the individual subjects were then added to the flat Stata file. The data fields included Gender (from Subject Table) and Height_(m), Weight_(kg), Smoker, Alcohol, Alcohol_Units/Week and ASA grade from the SSP Fitness Assessment Table. The Specialist Screening Practitioner (SSP) asks the participant questions on alcohol intake and smoking history as well as obtaining a height and weight prior to the first diagnostic test of the episode and these readings are recorded on BCSS. The Gender data field was complete with one record per unique Subject_ID. However, data fields in the SSP Fitness Assessment Table relate to an episode. There were therefore multiple sets of data for individual subjects. At this stage, all of these data were imported to Stata, creating up to six sets of personal details data per Subject_ID.

From the Diagnostic Test Table, the following data fields were imported pertaining to the screening episodes in the Stata file:

- Diag_Test_ID
- Test_Date
- Test_Type

A single screening episode could include up to nine diagnostic tests. The first Test_Date in the screening episode was imported as Screen_Test_Date. All data from Diag_Test_ID and Test_Type were imported and organised sequentially. Then additional fields on quality of examination were added to each Diag_Test_ID from the Endoscopic Test Table, to create data in the following format:

- Diag_test_ID1
- test_type1
- bowel_prep1
- extent1

Surveillance Episodes

The same data on each surveillance episode were then imported, again from the Diagnostic Test Table and Endoscopic Test Table. An individual subject may have attended up to five surveillance episodes and a single surveillance episode may comprise up to seven diagnostic tests. Therefore, surveillance episode data were arranged in the format detailed in appendix 1.3, using 'Su' as a prefix denoting a surveillance episode.

Blank surveillance episodes

It should be noted that a surveillance episode may exist in the Stata file, but contain no data. This scenario occurs where a surveillance Episode_ID (SuEpisode_ID) has been allocated, but no diagnostic test was performed in that episode (e.g. cancelled diagnostic test or subject did not attend). In this scenario, a subsequent surveillance episode may exist, and contain data.

Therefore, it was necessary to effectively discount these "blank" surveillance episodes so that the analysis variables described above represented the true sequence of surveillance episodes. To achieve this, the following processes were followed.

Creation of working variables

SuX_exists – any diagnostic test attended in corresponding surveillance episode (X = 1 to 5)

Su_count – count of SuX_exists

"Shuffling" surveillance episodes left

All analysis variables corresponding to surveillance episodes were affected by the blank surveillance episodes. For each analysis variable, the same process was followed and so a .do file was created in Stata for this purpose.

There are 31 theoretically possible sequences of surveillance episodes existing (2 to the power 5 minus 1 as 0-0-0-0-0 is not possible). In fact, 12 of these sequences do not occur in the file. The .do file was created to correct all of the 19 sequences which do occur. This .do file is based on the created variables SuX_exists, which is in turn based on a date existing anywhere in that surveillance episode. Throughout all 35 diagnostic tests (1_1 to 5_7) for all subjects, there are only two instances where a date is missing but a test did occur (both in Su1_1). These two Su1_exists variables were manually coded

correctly prior to running each variant of the .do file. This process is detailed in appendix 1.5.

Timing of diagnosis of cancer

As detailed above, the process of matching NCRAS and BCSS cancers highlighted that neither NCRAS nor BCSS cancer data includes all colorectal cancers affecting the screening population. Therefore, the most complete dataset of cancers in this cohort is the combined and cross-referenced NCRAS-BCSS cancer data. On this basis, analyses of cancer incidence were restricted to the time period for which these data were available. As detailed above, NCRAS data were interrogated for tumours diagnosed from 01/07/2006 until 31/12/2014.

The BCSS Cancer Table (refreshed) included cancers diagnosed up to 2017. However, all tumours diagnosed after 31/12/2014 were disregarded from CRC analysis on the basis that these data were incomplete without NCRAS data.

Follow-up in all analyses using cancer as an endpoint used an end of follow-up date of 30/9/2014. This date allowed a 3 month period until the end of complete cancer data (31/12/2014) in order to allow for variation in the documented date of diagnosis. For example, a surveillance episode could have commenced with a diagnostic test on 30/9/2014. This same surveillance episode could include more than one diagnostic test which may include more than one histological sampling, or further investigation with radiological imaging. Such a sequence of events may result in a colorectal cancer being

documented with a diagnosis date later than the first test date of the BCSS episode which ultimately resulted in the cancer diagnosis. The 3 month allowance for such scenarios was the time period used by the PHE Screening team to assign tumours to a BCSS episode during data cleaning.

On importing cancer data to the Stata analysis file, it was apparent that six subjects had a diagnosis of colorectal cancer prior to the start date of their screening episode in BCSS (Screen_Test_Date). This scenario occurs where an individual has been diagnosed with a colorectal cancer previously, but then participates in the BCSP, is found to have adenomas, and enters post-polypectomy surveillance. As the available NCRAS cancer data includes only tumours diagnosed from 01/07/2006, it is not known if other subjects have a prior diagnosis of colorectal cancer before entering the BCSP and post-polypectomy surveillance. For this reason, these six subjects are retained in the analysis dataset and the details of their prior cancers disregarded. Therefore, the analysis represents the true BCSP screening population with no exclusion of individuals on the basis of prior cancer diagnosis.

Explanatory variables

Effect on the outcomes of advanced adenomas and cancer at surveillance (including interval CRCs where appropriate) were assessed for the following variables. These were available directly from BCSS data fields or were created from data items recorded on the BCSS database:

1. Polyp-related factors
    i. Number of adenomas
    ii. Size of largest adenoma
        a) Presence vs absence of adenoma ≥20mm
        b) Presence vs absence of adenoma ≥10mm
    iii. Location of adenoma (proximal vs distal: defined as rectum to splenic flexure inclusive being distal.)
    iv. Presence of villous features
    v. HGD
    vi. Paris classification[5]
    vii. Piecemeal resection of any adenoma
2. Person-related factors
    i. Gender
    ii. Age
    iii. Smoking history
    iv. BMI
    v. Alcohol intake
    vi. ASA grade (American Society of Anaesthesiologists – grading of physical status based on multi-morbidities)
3. Diagnostic test factors
    i. Bowel prep quality

[5] *Polyp morphology described using the Paris classification: flat, sessile, or pedunculated (IIa/b/c, Is, Ip/sp).

ii. Incomplete examination

These variables (or the raw data which was used to create them) were available for the index screening episode and subsequent surveillance episodes. The variables were combined in different ways in the analysis to examine alternative risk stratification groups.

Deriving Analysis Variables

In order to allow analysis in Stata, further variables were created as detailed in appendix 1.4.

Cancer outcome analysis variables

As discussed above, analyses with cancer as the outcome must be time limited to allow for complete cancer data availability up to 31/12/2014. It was noted that the majority of documented CRCs were diagnosed at first surveillance, with few interval cancers: of 188 cases of CRC included in the final analysis, 140 (74.5%) were diagnosed at first surveillance and a further 16 (8.5%) at second or third surveillance. In order to avoid overestimating cancer-free survival time, qualification for CRC analysis required attendance at at least one surveillance episode by 30/9/2014. This had the additional effect of including at least one year of follow-up for each individual due to the surveillance interval of at least one year.

These criteria identified 28,468 eligible subjects of whom 188 were diagnosed with a CRC by the end of follow-up.

Where a CRC date of diagnosis occurred within 3 months of a BCSS episode date, the date of diagnosis was adjusted to match the BCSS episode date. CRC cases were then classified as being related to a BCSS episode (first surveillance, second surveillance, third surveillance), or to an interval (pre-first surveillance, first surveillance – second surveillance interval, etc.), or after the last attended BCSS episode (post-first surveillance, post-second surveillance).

Death data

BCSS data on dates of death were included for all study subjects. These data originate from NHAIS (National Health Application and Infrastructure Services) data.

Polyps

The Polyps Table of the original BCSS data extraction was the most complex to process for analysis. There were more than 360000 rows of data in this Excel sheet. Each Polyp_ID could have multiple corresponding rows of data. When a polyp is resected, a number of procedures may be performed: submucosal injection (1 row), hot snare polypectomy (1 row), a haemostatic technique such as application of a clip (1 row), tattooing for larger lesions (1 row).

A single polyp may also be documented at more than one diagnostic test within an episode. In such cases, a new Polyp_ID will be used although this refers to the same polyp. There are many possible reasons for documentation of a single polyp at multiple diagnostic tests: resection of a polyp may not be possible at

the first test at which the polyp is detected (CTC, endoscopic test while taking anticoagulant or antiplatelet medication, or specialist endoscopic skill required for resection of a complex polyp). Alternatively, a polyp may be resected incompletely and subsequent further resection performed within the same episode.

The PHE Screening Team provided the current rules used in the BCSS algorithm to determine when a polyp is counted as an adenoma (appendix 1.6). In summary, to be counted as an adenoma, a polyp must meet two primary criteria: have been resected, and to have histology in keeping with an adenomatous polyp. (Note that a resected polyp with no histology result will be assumed to have been an adenoma. This scenario may occur where a polyp is resected but the specimen not retrieved.)

Since January 2008, there has been a "secondary piece" field available in BCSS in order to flag where a further histology specimen is retrieved for the same polyp. Where used, this marks a Polyp_ID as a "secondary piece", but does not specify to which previous Polyp_ID this corresponds.

The full data cleaning method used is detailed in appendix 1.6.

The following description summarises the procedure followed in cleaning and formatting the polyp data for inclusion in the master analysis file. Firstly,

polyps to be excluded from analysis were identified: polyps which were non-neoplastic (inflammatory, lymphoid, Peutz-Jeghers) or not arising in the colorectum (anus, ileum, anastomosis). Secondly, extraneous data in the polyp file was identified: for example a submucosal injection, chromoscopy, or haemostatic technique performed as part of the polypectomy procedure.

Before exporting the selected polyp data to Stata®, the following data cleaning procedure was followed. There were 957 polyp Histology_IDs identified by the BCSS data extraction to correspond to a Polyp_ID with more than one histology record. These records represent fewer than 479 polyps (957 divided by two) with at least two histology records. Each of these records was reviewed to ensure that the most advanced histology findings were included for analysis: greatest size, greatest villous architecture, and highest grade of dysplasia. The most complete data regarding polypectomy for that Polyp_ID were also retained.

There were fifty-four polyps with a histology or endoscopic size of at least 100mm. It was considered that this size was more likely to represent a data entry error than a genuine measurement. Each of these records was reviewed to ensure that any more probable size for that Polyp_ID was used preferentially. However, for most of these records, the size of at least 100mm was retained as no alternative size had been entered.

The BCSS data extraction identified 1105 Polyp_IDs which were flagged as a "secondary piece" of a polyp already recorded at a previous diagnostic test (and therefore under a different Polyp_ID). There was no direct linkage between the multiple Polyp_IDs of these polyps and so individual review of each case was necessary. Each of these records was reviewed to include the most advanced histology recorded where histological diagnosis was either the same or a differing grade or architecture of the same polyp type. Therefore, a tubulovillous adenoma was accepted to be the same polyp as a tubular adenoma. However, a Polyp_ID marked as a secondary piece where no suitable polyp could identified as the "primary piece" at a previous diagnostic test, was left unchanged as a unique polyp. This could occur where the histological diagnosis did not match: such as a hyperplastic polyp where previous histology had shown an adenoma.

The resultant cleaned Excel® file was then exported to Stata®. A final size was created based on histology size where available (largest histology size where more than one entry exists), or (largest) endoscopic size if there was no histology size. Endoscopic size was also used in the case of piecemeal excision. The most detailed histological diagnosis was used for final histology. For example, 'tubulovillous adenoma' in preference to 'adenoma'.

A wide file was created with one record per Polyp_ID, and up to four sets of polyp data per record. These four sets of polyp data were amalgamated to

create a single record per polyp. The following rules were used. The modality was entered in the following descending hierarchy: ESD (endoscopic submucosal dissection), EMR (endoscopic mucosal resection), polypectomy, biopsy, tissue destruction (e.g. argon plasma coagulation), tattooing. A binary variable "resected" was included as '1' where '1' existed in any set of data for that polyp. In addition, polyps of up to 5mm in size where either biopsy or tissue destruction had been performed, were assumed to be resected and entered as '1'. This decision was taken as biopsy or tissue destruction of a diminutive polyp would be assumed to be effective polypectomy and so "resected = 0" was assumed to be a data entry error.

Statistical Analysis

General analytic approach: In the first instance, descriptive analyses were undertaken in terms of numbers and percentages. Subsequently univariable and multivariable analyses were performed, using appropriate statistical models, to evaluate the effects of each variable on surveillance outcome. Specifically, the variables described above were assessed for effect on the finding of advanced adenomas at first surveillance, and on overall cancer incidence.

Person-years at risk (PYR): Person years at risk was calculated for each individual in the CRC analysis. PYR was defined as the time from date of the

(first) diagnostic test associated with the index screening episode to the earliest of: date of diagnosis of colorectal cancer, death or end of follow-up (30/9/2014).

Missing data: A category of unknown was created where data for a specific variable were unknown. Multiple imputation methods were not used.

Descriptive analyses: Initially the characteristics of the study cohort were summarised in terms numbers and percentages. Surveillance pathways were described separately for the IR and HR groups. The data were summarised in terms of the numbers of individuals who had a first surveillance test, second surveillance test, and so on and described in terms of numbers and percentages (of the cohort, or subgroup). Numbers and percentages reaching each surveillance outcome were documented stratified by screening risk category:

- CRC / HR / IR / LR / no adenoma at 1st surveillance
- CRC / advanced adenoma / non-advanced adenoma / no adenoma at 1st surveillance
- CRC / advanced adenoma / non-advanced adenoma / no adenoma at 2nd surveillance

Incidence rates: The CRC incidence rate per 100,000 population was computed (i.e. numbers of individuals who had CRC diagnosed divided by the summed PYR for all individuals) for the entire dataset, and by IR/HR subgroup.

Comparisons of the CRC incidence rate by key explanatory variables (e.g. sex, age-group, BMI) was also undertaken.

Univariable & Multivariable analyses

Initially the analysis considered individuals grouped according to the BCSP definitions (i.e. intermediate and high risk). It was then repeated classifying individuals into groups based on individual polyp data:

1. Total of 1 adenoma, of at least 10mm in size
2. Total of 2 adenomas, with at least one of at least 10mm in size
3. Total of 3 adenomas, with at least one of at least 10mm in size
4. Total of 4 adenomas, with at least one of at least 10mm in size
5. Total of at least 5 adenomas, with at least one of at least 10mm in size
6. Total of 3 adenomas, all being less than 10mm in size
7. Total of 4 adenomas, all being less than 10mm in size
8. Total of at least 5 adenomas, all being less than 10mm in size

It should be noted that the dataset included individuals with apparently complete polyp data showing only 1 or 2 adenomas of <10mm size at screening (n=877). These individuals were excluded from analysis as the adenoma characteristics indicating the need for surveillance could not be identified in this group.

In the univariable analyses, for each analysis variable, cancer incidence rates were compared between subgroups using the log-rank test for equality of survivor functions.

Cox proportional hazards regression was performed for CRC analyses. This allowed analysis based on person years at risk. For analyses of advanced adenoma at first surveillance, logistic regression was used as the diagnosis of AA could occur only at the time of first surveillance, not at other time points. It must be noted that this approach does not take account of the timing of first surveillance. Therefore, when comparing individuals classified as high risk with intermediate risk (as in the univariate and multivariate analyses performed here), it must be assumed that findings would be similar whether first surveillance is performed at a one or three year interval. This assumption is in keeping with the understanding of adenoma progression being a slow process.

Many published studies have used an outcome of Advanced Colorectal Neoplasia (ACN) as an endpoint, defined as the occurrence of either CRC or AA. This approach treats the outcome of cancer as equivalent to a (pre-cancerous) adenoma, which is clinically incorrect and so has not been used in the analyses presented in this thesis. However, for the purposes of comparison with published studies, a logistic regression analysis for ACN at first surveillance as an outcome was performed. In summary, the results of this analysis mirrored that of the logistic regression for AA at first surveillance. The addition of cases of CRC at first surveillance to AA at first surveillance had no significant effect on the analysis outcome due to the low absolute number of CRC cases (n=180) compared to cases of AA at first surveillance (n=4483).

Initially univariable hazard ratios, with 95% confidence intervals, were computed for each analysis variable. Subsequently multivariable models were built. Initially variables with a p value of <0.1 (Wald test) in the univariable analysis were considered for inclusion in the multivariable model. These were fitted simultaneously and their contribution to the model assessed. Variables which were not significant ($p<0.05$) were dropped.

Multicollinearity occurs when there are high correlations among predictor variables, leading to unreliable and unstable estimates of regression coefficients. A common test for multicollinearity is the Variance Inflation Factor (VIF). The VIF was calculated in Stata. This is calculated by performing linear regression of each predictor on all the other predictors, then obtaining the R2 from that regression. The VIF is equal to 1/(1-R2). A VIF value is always ≥1 (with no upper limit) and estimates to what extent the variance of a coefficient is increased by linear dependence with another factor. All VIF values calculated for the final models were <1.1, indicating no significant multicollinearity.

Variables not significant on univariate analyses were then assessed for whether they should be included in the model.

For each variable in the model a test for proportionality of hazards was performed in Stata (using Schoenfeld residuals), testing the null hypothesis of

zero slope, which is equivalent to testing that the log hazard-ratio function is constant over time.

Goodness of fit of each model was assessed in Stata using the Hosmer-Lemeshow test, which assesses whether or not the observed event rates match expected event rates in subgroups of the model population.

There were differing potential approaches to incorporating some factors in the multivariate analyses. For example: number of adenomas alone, size of largest adenoma alone, or a subgroup classification based on the number and size of adenomas. A model could include any of these factors if statistically significant, but it would not be logical to include, for example, more than one variable related to size of adenoma. Therefore, the Akaike information criterion (AIC) and Bayesian information criterion (BIC) were calculated in Stata for the multivariate models being considered. The AIC and BIC estimate the quality of each model, relative to each of the other models and provide a means for model selection. These measures are based on information theory, offering an estimate of the relative information lost when a given model is used and so deals with the trade-off between the goodness of fit of the model and the simplicity of the model.

Over the time of the screening programme, changes have been made in recording of data. The effect on the results of potentially relevant changes were explored by restricting the analyses by year of initial screening test.

Ethical consideration

This study was given Durham University ethics approval by proportionate review, and was approved by the BCSP Research Committee and the North Tees and Hartlepool NHS Foundation Trust Research Committee.

This study did not involve any direct contact with screening participants and had no impact on the care of participants. Therefore, formal NHS ethics approval was not required. Confidentiality of the participants was ensured by anonymization of the data prior to its transfer from Public Health England. This was achieved by data on each subject being linked before identifiers are removed (NHS number, date of birth). Each subject was then be assigned a unique study number by the data processor at Public Health England before the fully anonymized data was transmitted securely to the investigator.

CHAPTER 5 – Data Analysis Results

Section 1 - Descriptive data

From the start of the programme in 2006 until the 3rd of January 2017, the BCSP in England sent out 34,969,006 FOBt kits. 20,317,133 kits were returned, of which 360,464 were defined as abnormal. Overall, 56.3% of the invited population were screened by FOBt, with a positivity rate of 1.95%. However, there was wide variation in uptake; prevalent round uptake was 36.9% overall with a positive rate of 2.22% (first invitation prevalent round uptake was 52.2%). Incident round uptake was 85.9% with a positive rate of 1.77%.

Over the same time period, 416,052 diagnostic tests were attended. 377,735 (90.8%) of these were colonoscopies. It should be noted that a single episode may consist of more than one diagnostic test.

Screening episode outcome is detailed in Table 3 below.

Outcome	Overall	
Cancer	8.67%	
High risk	9.73%	Therefore **24.65%** of those attending a screening diagnostic test qualify for post-polypectomy surveillance.
Intermediate risk	14.92%	
Low risk	18.38%	
No adenoma (normal / abnormal)	45.42%	
No result / no histology	2.87%	
TOTAL	**100%**	

Table 3 - Screening outcome

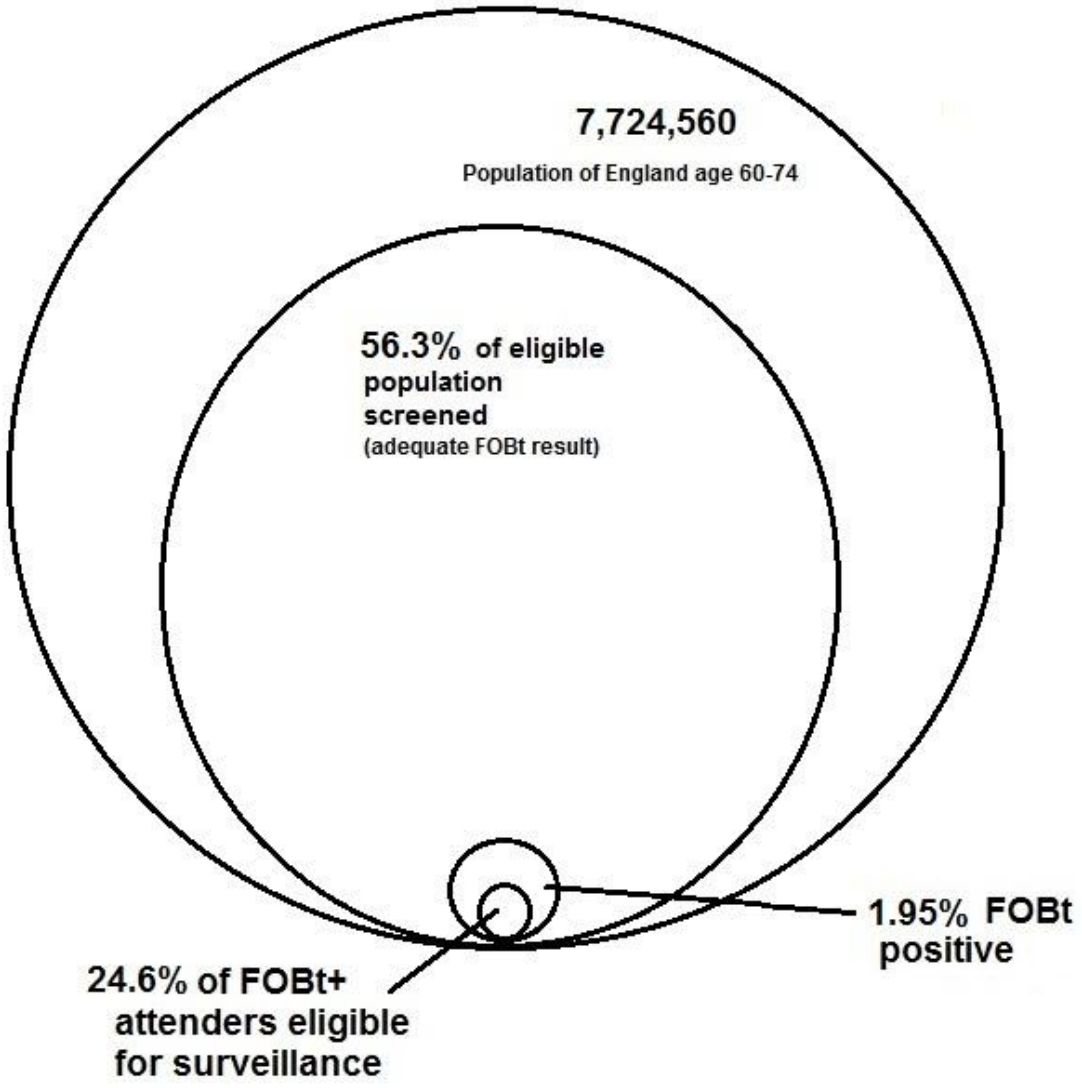

Figure 3 - Screened population

As illustrated in Figure 3 above, the population studied in this thesis represents a small proportion of the overall population eligible for screening. The resident population of England aged 60 to 74 totalled 7.72 million (Census, 2011). BCSP reports show that 56.3% of the eligible population had been screened adequately by FOBt. As detailed above, 1.95% of FOBt results are positive, resulting in an invitation to a diagnostic test (colonoscopy). Of those attending for a diagnostic test, almost 1 in 4 have findings qualifying for post-polypectomy surveillance.

The data analysed for this thesis was extracted on 3rd January 2017 and covered the entire time period from the start of the programme in 2006 until the date of extraction. Only data pertaining to those individuals who had attended a surveillance episode was included. A total of 43,131 unique subjects were included in the final analyses. Analysis of the demographics of the included subjects showed a significant preponderance of male subjects at 70.5% (n=30414). Of the included baseline screening episodes, 51.9% (n=22391) were classified as intermediate risk and 48.1% (n=20740) as high risk.

The following descriptive data and analyses in Sections 1 and 2 pertain to the full cohort for polyp analysis. This cohort (n=43,131) comprises the full analysis dataset after exclusion of subjects with incomplete histology data due to first surveillance occurring after 14/12/2016 (n=143) and those not reaching

intermediate or high risk criteria at screening according to polyp data available from BCSS (n=877).

The CRC analysis cohort is a subset of the above polyp analysis cohort and is described in Section 3.

There were a total of 62,979 surveillance episodes attended, including over 119,000 screening and surveillance colonoscopies performed. 25,973 (60.2%) surveillance subjects completed only one surveillance episode during the study period. 17,158 (39.8%) completed at least two surveillance episodes, with up to five surveillance episodes being attended by some (n=15) subjects.

Screening episodes:

Age <65 (range 57-64):

A total of 19876 subjects fell into this age group at screening, of whom 14141 (71.1%) were male and 5735 (28.9%) female. Overall, 8769 (44.1%) of this age group were categorised as high risk, and 11107 (55.9%) intermediate risk. A higher proportion of males were classified as high risk compared to females. 2041 (35.6%) females were high risk and 3694 (64.4%) intermediate. 6728 (47.6%) males were high risk and 7413 (52.4%) intermediate.

Age 65-69:

A total of 18684 subjects fell into this age group at screening, of whom 13071 (70.0%) were male and 5613 (30.0%) female. Overall, 8868 (47.5%) of this age group were categorised as high risk, and 9816 (52.5%) intermediate risk. A higher proportion of males were classified as high risk compared to females. 2230 (39.7%) females were high risk and 3383 (60.3%) intermediate. 6638 (50.8%) males were high risk and 6433 (49.2%) intermediate.

Age >69:

A total of 4571 subjects fell into this age group at screening, of whom 3202 (70.1%) were male and 1369 (29.9%) female. Overall, 3103 (67.9%) of this age group were categorised as high risk, and 1468 (32.1%) intermediate risk. A higher proportion of males were classified as high risk compared to females. 824 (60.2%) females were high risk and 545 (39.8%) intermediate. 2279 (71.2%) males were high risk and 923 (28.8%) intermediate.

When categorised by age and sex, it is noted that a male preponderance persists across all ages in the screening programme. High risk findings occurred more frequently in males and frequency increased with age.

One individual was aged less than 59 at the time of screening: age 57 years. A small number (n=32) of subjects aged over 74 underwent screening. This can

occur when an individual chooses to "opt-in" to screening outside the standard age range of 60-74 years.

Surveillance episodes:

The increasing number of surveillance episodes being performed year on year is illustrated in Figure 4. Five years after the start of the screening programme, in 2011, a total of 5,465 episodes were completed. Five years later, in 2016, ten years after the start of the programme, this figure rose 1.5 fold to 13,698.

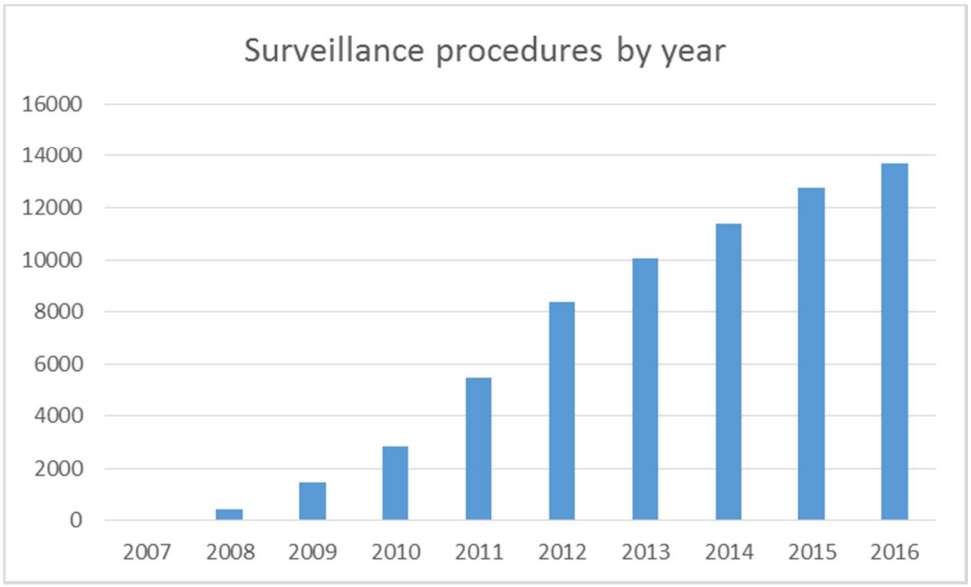

Figure 4 Surveillance episodes by year

By outcome:

Overall, the findings at surveillance demonstrate the most frequent outcome was no further adenoma being found and the least frequent outcome was CRC.

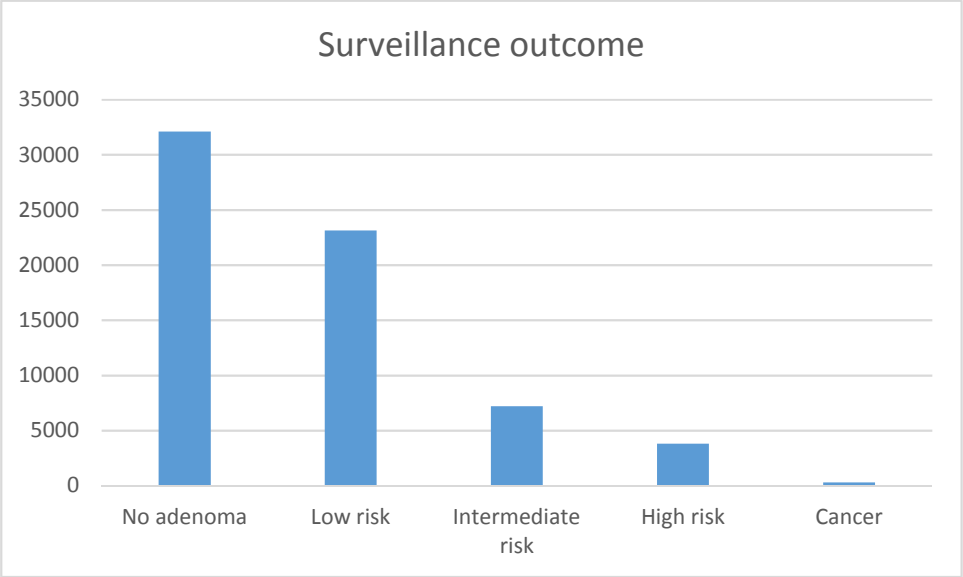

Figure 5 Surveillance outcome

Number of surveillance episodes by age group

Surveillance episodes were carried out most frequently in the 65-69 age group. This is in keeping with the expected surveillance interval after intermediate or high risk findings at screening performed age 60-64 (prevalent round).

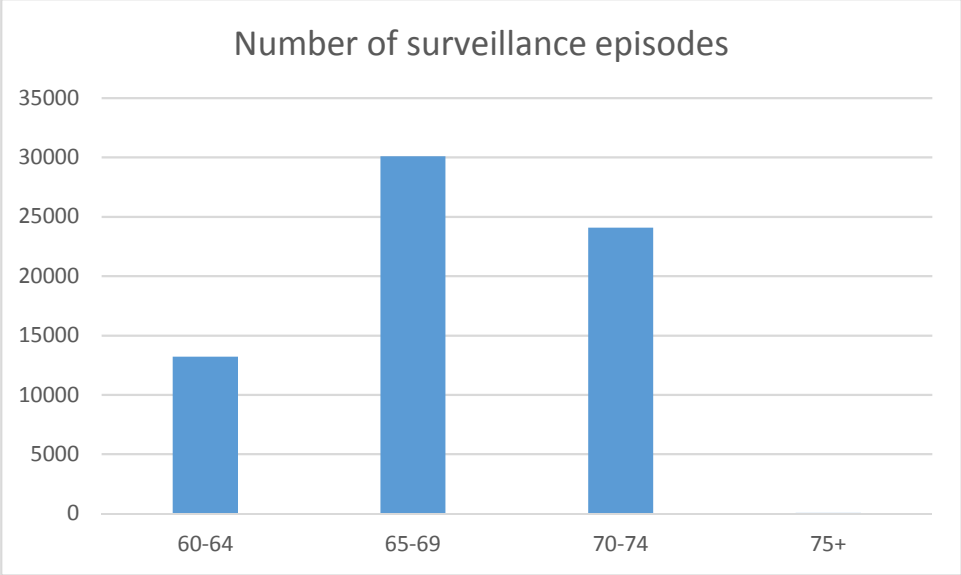

Figure 6 Surveillance episodes by age

The following section will present surveillance outcomes in detail.

Section 2 – Analysis cohort

Intermediate risk at screening

The polyp analysis cohort included 22,391 subjects with intermediate risk findings at screening according to their BCSS classification: 14,769 male (66.0%) and 7,622 female (34.0%). 11,107 (49.6%) were aged <65 years at screening, 9,816 (43.8%) aged 65-69, and 1,468 (6.6%) were aged over 69 years.

Baseline findings according to polyp data	N	% of "IR" analysis cohort	
Single adenoma of ≥10mm	11181	49.9	
2 adenomas, largest ≥10mm	6553	29.3	
3 adenomas, all <10mm	2096	9.4	
4 adenomas, all <10mm	948	4.2	
5 or more adenomas, all <10mm ("HR")	93	0.4	These 1238 individuals, comprising 5.5% of those categorised as intermediate risk, were found to have polyp data which would be defined as high risk.
3 adenomas, largest ≥10mm ("HR")	651	2.9	
4 adenomas, largest ≥10mm ("HR")	290	1.3	
5 or more adenomas, largest ≥10mm ("HR")	204	0.9	
Unknown	375	1.7	
Total	**22391**	**100**	

Table 4 - polyp findings IR screening

Of a total of 1,238 appearing to meet criteria for high risk ("HR") at screening, most attended first surveillance at a one year interval:

1st surv interval	N	%
6 – 18m	662	53.5
18m – 2.5y	143	11.6
2.5 – 3.5y	383	30.9
>3.5y	50	4.0
TOTAL	**1238**	**100**

Table 5 - 1st surv interval for IR with HR polyp data

Of the total intermediate risk analysis cohort of 22,391, there were 1,530 individuals (6.8%) who attended first surveillance at an interval of less than 2.5 years. Among this "early surveillance" group, 522 (34.1%) had an adenoma of ≥20mm at screening and a further 730 (47.7%) had an adenoma of 10-19mm at screening. Therefore, it is possible that a one year interval to first surveillance was planned according to protocols for the majority of this group.

		Female: 7622 (34.0%)		Male: 14769 (66.0%)		Total
		N	% of F	N	% of M	
BMI	**<18.5**	65	0.9	47	0.3	**112**
	18.5 – 24.9	2043	26.8	2998	20.3	**5041**
	25.0 – 29.9	2610	34.2	6368	43.1	**8978**
	30.0 – 39.9	2049	26.9	4040	27.4	**6089**
	≥40.0	295	3.9	278	1.9	**573**
	Unknown	560	7.3	1038	7.0	**1598**
Smoking	**Y**	888	11.7	1796	12.2	**2684**
	N	4568	59.9	6814	46.1	**11382**
	Ex-smoker	2149	28.2	6105	41.3	**8254**
	Unknown	17	0.2	54	0.4	**71**
Alcohol	**Y**	4532	59.5	11654	78.9	**16186**
	N	3090	40.5	3115	21.1	**6205**
Surv episodes	**1**	5162	67.7	9719	65.8	**14881**
	2	2383	31.3	4793	32.5	**7176**
	3	76	1.0	245	1.7	**321**
	4	1	0.0	11	0.0	**12**
	5	0	0.0	1	0.0	**1**

Table 6 - personal details, IR screening

Interval to 1st surveillance (IR screening only):

A small percentage (5.1%) of this cohort attended 1st surveillance at a shorter interval than expected at 6 – 18 months after baseline (n = 1148). A very small number, 382 (1.7%), attended 18 months – 2.5 years after baseline. The large majority, 19944 (89.1%) attended on time at an interval of 2.5 – 3.5 years. A further 917 (4.1%) attended first surveillance more than 3.5 years after baseline screening.

High risk at screening

The polyp analysis cohort included 20,740 subjects with high risk findings at screening according to BCSS their classification: 15,645 male (75.4%) and 5,095 female (24.6%). 8,769 (42.3%) were aged <65 years at screening, 8,868 (42.8%) aged 65-69, and 3,103 (15.0%) were aged over 69 years.

Baseline findings according to polyp data	**N**	**% of "HR" analysis cohort**	
Single adenoma of ≥10mm ("IR")	1216	5.9	2930 (14.1%) individuals categorised as high risk had polyp data in keeping with intermediate risk categorisation
2 adenomas, largest ≥10mm ("IR")	1464	7.1	
3 adenomas, all <10mm ("IR")	125	0.6	
4 adenomas, all <10mm ("IR")	125	0.6	
5 or more adenomas, all <10mm	2215	10.7	
3 adenomas, largest ≥10mm	5675	27.4	
4 adenomas, largest ≥10mm	3407	16.4	
5 or more adenomas, largest ≥10mm	6317	30.5	
Unknown	196	1.0	
Total	**20740**	**100**	

Table 7 - polyp findings at HR screening

As seen in those categorised by BCSS as "intermediate risk", there was a small proportion of the cohort where polyp data indicated "high risk" criteria were not met.

Of 2,930 individuals categorised as high risk by BCSS, but with polyp data showing an intermediate risk baseline, 1,724 (58.8%) had a largest adenoma of ≥20mm at baseline. A further 956 (32.6%) had a largest adenoma of 10-19mm.

		Female		**Male**		**Total**	**% of total**
		N	**% of F**	**N**	**% of M**		
BMI	**<18.5**	74	1.5	52	0.3	**126**	**0.6**
	18.5 – 24.9	1264	24.8	2998	19.2	**4262**	**20.5**
	25.0 – 29.9	1609	31.6	6422	41.1	**8031**	**38.7**
	30.0 – 39.9	1530	30.0	4705	30.1	**6235**	**30.1**
	≥40.0	258	5.1	367	2.4	**625**	**3.0**
	Unknown	360	7.1	1101	7.0	**1461**	**7.0**
Smoking	**Y**	822	16.1	2772	17.7	**3594**	**17.3**
	N	2807	55.1	6325	40.4	**9132**	**44.0**
	Ex-smoker	1450	28.5	6495	41.5	**7945**	**38.3**
	Unknown	16	0.3	53	0.3	**69**	**0.3**
Alcohol	**Y**	3007	59.0	12494	79.9	**15501**	**74.7**
	N	2088	41.0	3151	20.1	**5239**	**25.3**
Surv episodes	**1**	2946	57.8	8146	52.1	**11092**	**53.5**
	2	1693	33.2	5807	37.1	**7500**	**36.2**
	3	427	8.3	1541	9.9	**1968**	**9.5**
	4	25	0.5	141	0.9	**166**	**0.8**
	5	4	0.1	10	0.1	**14**	**0.07**

Table 8 - personal details, HR screening

Interval to first surveillance (HR screening only)

The overwhelming majority of individuals attending for first surveillance in the high risk category attended at the correct time interval: 19077 (92.0%) at 11 to 18 months. A few: 102 (0.5%), individuals attended at an interval of less than 11 months. 7.5% (1560 individuals) attended after an interval of greater than 18 months.

Surveillance pathways followed with surveillance outcome expressed as percentages

IR – BCSS surveillance outcome and intervals to subsequent surveillance

In the following tables, results are presented for individuals categorised to have intermediate risk at baseline.

OF IR SCREENING:

1st surv outcome	N	% (of IR screening)	PLAN	Actual 2nd surv interval		
No polyps	12567	56.1	3y	<2.5y	11	SEE **Error! Reference source not found.**
				2.5-3.5y	4061	
				>3.5y	91	
				No 2nd surv	**8404**	
LR	7230	32.3	3y	<2.5y	2	SEE **Error! Reference source not found.**
				2.5-3.5y	2164	
				>3.5y	64	
				No 2nd surv	**5000**	
IR	1734	7.7	3y	<2.5y	28	SEE **Error! Reference source not found.**
				2.5-3.5y	519	
				>3.5y	12	
				No 2nd surv	**1175**	
HR	738	3.3	1y	<11m	6	SEE **Error! Reference source not found.**
				11-18m	504	
				>18m	46	
				No 2nd surv	**182**	
Cancer	97*	0.4				
TOTAL	22366	99.9**				

Table 9

*Note date of diagnosis of cancer was within 3m of 1st surv date in 91 cases and >3m later in 6 cases.

**Note remaining 0.1% have "no result" for 1st surveillance.

In this large cohort of 22366 individuals, 3.3% had high risk and 7.7% intermediate risk at first surveillance. Almost 9 in 10 (88.4%) had no or low risk at first surveillance.

IR SCREENING THEN NO POLYPS 1ST SURVEILLANCE

2nd surv outcome	N	% (of those attended 2nd surv)	PLAN	Actual 3rd surv interval		3rd surv outcome
No polyps	2718	65.4	**STOP**	<2.5y	0	8 no polyps 3 LR 1 HR
				2.5-3.5y	12	
				>3.5y	0	
				No 3rd surv	**2706**	
LR	1187	28.6	3y	<2.5y	0	13 no polyps 6 LR 2 IR
				2.5-3.5y	21	
				>3.5y	0	
				No 3rd surv	**1166**	
IR	163	3.9	3y	<2.5y	4	5 no polyps 4 LR 1 IR 1 HR
				2.5-3.5y	7	
				>3.5y	0	
				No 3rd surv	**152**	
HR	70	1.7	1y	<11m	0	18 no polyps 18 LR 2 IR 2 HR
				11-18m	36	
				>18m	4	
				No 3rd surv	**30**	
Cancer	14*	0.3				
TOTAL	4152	99.9				

Table 10

*Note date of diagnosis of cancer was within 3m of 2nd surveillance in 13 cases and >3m later in 1 case.

Of all groups attending second surveillance, the lowest percentage of both high (1.7%) and intermediate (3.9%) risk were seen in this cohort where intermediate risk had been found at baseline and no further adenoma at first surveillance.

IR SCREENING THEN LR 1ST SURVEILLANCE

2nd surv outcome	N	% (of those attended 2nd surv)	PLAN	Actual 3rd surv interval		3rd surv outcome
No polyps	1097	49.2	3y	<2.5y	1	16 no polyps 8 LR 2 IR 1 HR
				2.5-3.5y	26	
				>3.5y	0	
				No 3rd surv	**1070**	
LR	856	38.4	3y	<2.5y	0	5 no polyps 7 LR 1 IR
				2.5-3.5y	13	
				>3.5y	0	
				No 3rd surv	**843**	
IR	175	7.8	3y	<2.5y	1	1 no polyps 1 HR
				2.5-3.5y	1	
				>3.5y	0	
				No 3rd surv	**173**	
HR	83	3.7	1y	<11m	1	13 no polyps 18 LR 7 IR 2 HR
				11-18m	37	
				>18m	2	
				No 3rd surv	**43**	
Cancer	5*	0.2				
TOTAL	2216	99.4				

Table 11

*All diagnosed within 3m of 2nd surveillance.

Nearly half of this cohort were found to have no further polyp at second surveillance and less than 4% had high risk findings at second surveillance.

IR SCREENING THEN IR 1ST SURVEILLANCE

2nd surv outcome	N	% (of those attended 2nd surv)	PLAN	Actual 3rd surv interval		3rd surv outcome
No polyps	245	43.8	3y	<2.5y	0	8 No polyps 4 LR 1 IR
				2.5-3.5y	13	
				>3.5y	0	
				No 3rd surv	**232**	
LR	200	35.8	3y	<2.5y	0	2 no polyps 4 LR 2 IR 1 HR
				2.5-3.5y	9	
				>3.5y	0	
				No 3rd surv	**191**	
IR	78	14.0	3y	<2.5y	1	1 no polyps 1 LR
				2.5-3.5y	1	
				>3.5y	0	
				No 3rd surv	**76**	
HR	33	5.9	1y	<11m	0	6 no polyps 7 LR 2 IR 1 HR
				11-18m	15	
				>18m	1	
				No 3rd surv	**17**	
Cancer	1*	0.2				
TOTAL	557	99.6				

Table 12

*Diagnosed within 3m of 2nd surv.

Although this cohort had been categorised as intermediate risk at both screening and first surveillance, almost 79.6% had second surveillance findings of either no polyps or low risk category adenomas. It must be noted, however, that this group is a relatively small cohort of 557 individuals.

IR SCREENING THEN HR 1ST SURVEILLANCE

2nd surv outcome	N	% (of those attended 2nd surv)	PLAN	Actual 3rd surv interval		3rd surv outcome
No polyps	196	35.3	3y	<2.5y	0	22 no polyps 8 LR 4 IR 1 HR **1 cancer**
				2.5-3.5y	36	
				>3.5y	0	
				No 3rd surv	**160**	
LR	232	41.7	3y	<2.5y	1	12 no polyps 20 LR 5 IR 6 HR
				2.5-3.5y	42	
				>3.5y	0	
				No 3rd surv	**189**	
IR	68	12.2	3y	<2.5y	1	3 no polyps 3 LR 3 IR 2 HR
				2.5-3.5y	10	
				>3.5y	0	
				No 3rd surv	**57**	
HR	56	10.0	1y	<11m	0	8 no polyps 14 LR 9 IR 7 HR
				11-18m	36	
				>18m	2	
				No 3rd surv	**18**	
Cancer	1*	0.2				
TOTAL	553	99.5				

Table 13

*Diagnosed within 3m of 2nd surv.

Of 553 individuals attending second surveillance after intermediate risk and then high risk previously, 77.0% had no or low risk at second surveillance and 22.2% were again found to have intermediate or high risk. These findings are similar to the group attending second surveillance after high risk and then intermediate risk previously (see Table 17).

HR – BCSS surveillance outcome and intervals to subsequent surveillance

1st surv outcome	N	% (of HR screening)	PLAN	Actual 2nd surv interval		
No polyps	8112	39.1	3y	<2.5y	10 (0.3%)	SEE Table 15
				2.5-3.5y	3476 (96.6%)	
				>3.5y	111 (3.1%)	
				No 2nd surv	**4515**	
LR	7748	37.4	3y	<2.5y	8 (0.2%)	SEE Table 16
				2.5-3.5y	3210 (96.8%)	
				>3.5y	97 (2.9%)	
				No 2nd surv	**4433**	
IR	3121	15.0	3y	<2.5y	58 (3.8%)	SEE Table 17
				2.5-3.5y	1376 (91.1%)	
				>3.5y	77 (5.1%)	
				No 2nd surv	**1610**	
HR	1639	7.9	1y	<11m	8 (0.7%)	SEE Table 18
				11-18m	1119 (91.7%)	
				>18m	93 (7.6%)	
				No 2nd surv	**419**	
Cancer	102*	0.5				
TOTAL	20722	99.9**				

Table 14

*Note date of diagnosis of cancer was within 3m of 1st surveillance in 92 cases, >3m later in 9 cases and >3m before in 1 case.

**Note <0.1% (n=18) have "no result" for 1st surveillance.

In those categorised as high risk at index screening episode, more than three in four (76.5%) first surveillance episodes found either no adenoma or low risk findings. Greater than 91% of those attending for second surveillance attended on time (<6 months after due date).

HR SCREENING THEN NO POLYPS 1ST SURVEILLANCE

2nd surv outcome	N	% (of those attended 2nd surv)	PLAN	Actual 3rd surv interval		3rd surv outcome
No polyps	1866	52.1	3y	<2.5y	0	173 no polyps 86 LR 20 IR 3 HR **2 cancer**
				2.5-3.5y	279	
				>3.5y	6	
				No 3rd surv	**1581**	
LR	1268	35.4	3y	<2.5y	0	77 no polyps 70 LR 20 IR 8 HR **1 cancer**
				2.5-3.5y	174	
				>3.5y	4	
				No 3rd surv	**1090**	
IR	277	7.7	3y	<2.5y	6	14 no polyps 17 LR 7 IR 8 HR
				2.5-3.5y	40	
				>3.5y	1	
				No 3rd surv	**230**	
HR	153	4.3	1y	<11m	0	28 no polyps 37 LR 20 IR 6 HR
				11-18m	86	
				>18m	5	
				No 3rd surv	**62**	
Cancer	19*	0.5				
TOTAL	3583	100.0				

Table 15

*All diagnosed within 3m of date of 2nd surveillance.

In those with no adenoma at first surveillance, 87.5% were found to have either no adenoma or low risk findings at second surveillance. As at first surveillance, CRC was diagnosed in 0.5%. A small proportion of the total group had attended for third surveillance during the study period.

HR SCREENING THEN LR 1ST SURVEILLANCE

2nd surv outcome	N	% (of those attended 2nd surv)	PLAN	Actual 3rd surv interval		3rd surv outcome
No polyps	1253	37.8	3y	<2.5y	3	76 no polyp 76 LR 20 IR 11 HR **2 cancer**
				2.5-3.5y	179	
				>3.5y	4	
				No 3rd surv	**1067**	
LR	1372	41.4	3y	<2.5y	0	73 no polyp 76 LR 16 IR 17 HR
				2.5-3.5y	181	
				>3.5y	3	
				No 3rd surv	**1188**	
IR	443	13.4	3y	<2.5y	3	17 no polyp 26 LR 14 IR 6 HR **1 cancer**
				2.5-3.5y	62	
				>3.5y	0	
				No 3rd surv	**376**	
HR	232	7.0	1y	<11m	1	42 no polyp 52 LR 12 IR 20 HR
				11-18m	120	
				>18m	6	
				No 3rd surv	**105**	
Cancer	10*	0.3				
TOTAL	3310	100.0				

Table 16

*Note date of diagnosis of cancer was within 3m of 2nd surveillance in 9 cases and >3m later in 1 case.

In those low risk at first surveillance, nearly four in five of those attending second surveillance were found to have either no adenoma or low risk findings again.

HR SCREENING THEN IR 1ST SURVEILLANCE

2nd surv outcome	N	% (of those attended 2nd surv)	PLAN	Actual 3rd surv interval		3rd surv outcome
No polyps	479	31.8	3y	<2.5y	0	78 no polyps 42 LR 14 IR 9 HR **1 cancer**
				2.5-3.5y	140	
				>3.5y	5	
				No 3rd surv	**334**	
LR	600	39.9	3y	<2.5y	0	56 no polyps 62 LR 15 IR 5 HR
				2.5-3.5y	135	
				>3.5y	4	
				No 3rd surv	**461**	
IR	255	16.9	3y	<2.5y	6	19 no polyps 26 LR 10 IR 4 HR
				2.5-3.5y	51	
				>3.5y	2	
				No 3rd surv	**196**	
HR	164	10.9	1y	<11m	0	21 no polyps 47 LR 16 IR 24 HR
				11-18m	105	
				>18m	3	
				No 3rd surv	**56**	
Cancer	7*	0.5				
TOTAL	1505	100.0				

Table 17

*All diagnosed within 3m of 2nd surveillance.

Of 1505 individuals attending second surveillance after high risk and then intermediate risk previously, 71.7% had no or low risk at second surveillance and 27.5% were again found to have intermediate or high risk.

HR SCREENING THEN HR 1ST SURVEILLANCE

2nd surv outcome	N	% (of those attended 2nd surv)	PLAN	Actual 3rd surv interval		3rd surv outcome
No polyps	269	22.1	3y	<2.5y	1	43 no polyps 41 LR 20 IR 13 HR
				2.5-3.5y	111	
				>3.5y	5	
				No 3rd surv	**152**	
LR	484	39.7	3y	<2.5y	1	37 no polyps 70 LR 33 IR 28 HR **1 cancer**
				2.5-3.5y	164	
				>3.5y	4	
				No 3rd surv	**315**	
IR	257	21.1	3y	<2.5y	7	18 no polyps 25 LR 31 IR 20 HR **1 cancer**
				2.5-3.5y	91	
				>3.5y	1	
				No 3rd surv	**158**	
HR	201	16.5	1y	<11m	0	11 no polyps 53 LR 30 IR 52 HR
				11-18m	133	
				>18m	15	
				No 3rd surv	**53**	
Cancer	8*	0.7				
TOTAL	1219	100.0				

Table 18

*Note date of diagnosis of cancer was within 3m of 2nd surveillance in 5 cases and >3m later in 2 cases.

As may have been anticipated, the greatest percentage of high risk and intermediate risk at second surveillance were observed in those attending after high risk at both baseline and first surveillance. Of 1219 individuals in this group, 201 (16.5%) again had high risk and more 257 (21.1%) had intermediate risk. In total, more than 1 in 3 (37.6%) of this group had intermediate or high risk at second surveillance.

Surveillance outcome as highest neoplasia based on polyp data

In this section, results are again presented separately for individuals categorised to have high risk or intermediate risk at baseline. In these tables, surveillance outcome is reported by most advanced neoplasia (not risk category).

IR – AA at surveillance outcome and intervals to subsequent surveillance

OF IR SCREENING:

1st surv outcome	n	% (of IR screening)	Actual 2nd surv interval		2nd surv outcome
No adenoma	12567	56.1	<2.5y	11	2718 no adenoma (65.3%) 1225 NAA (29.4%) **195 AA (4.7%)** 13 cancer (0.3%)
			2.5-3.5y	4061	
			>3.5y	91	
			No 2nd surv	**8404**	
NAA	7904	35.3	<18m	171	1164 no adenoma (46.2%) 1175 NAA (46.7%) **161 AA (6.4%)** 3 cancer (0.1%)
			18m – 2.5y	13	
			2.5-3.5y	2267	
			>3.5y	66	
			No 2nd surv	**5387**	
AA	**1798**	**8.0**	<18m	362	374 no adenoma (45.2%) 354 NAA (42.8%) **91 AA (11.0%)** 4 cancer (0.5%)
			18m – 2.5y	36	
			2.5-3.5y	420	
			>3.5y	10	
			No 2nd surv	**970**	
Cancer	97*	0.4			
TOTAL	22366	99.9**			

Table 19

*Note date of diagnosis of cancer was within 3m of 1st surv date in 91 cases and >3m later in 6 cases.

**Note remaining 0.1% have "no result" for 1st surveillance.

HR – AA at surveillance outcome and intervals to subsequent surveillance

OF HR SCREENING:

1st surv outcome	N	% (of HR screening)	Actual 2nd surv interval		2nd surv outcome
No adenoma	8112	39.1	<2.5y	10 (0.3%)	1866 no adenoma (51.9%) 1412 NAA (39.3%) **286 AA (8.0%)** 19 cancer (0.5%)
			2.5-3.5y	3476 (96.6%)	
			>3.5y	111 (3.1%)	
			No 2nd surv	**4515**	
NAA	9963	48.0	<18m	546	1557 no adenoma (33.7%) 2527 NAA (54.7%) **512 AA (11.1%)** 16 cancer (0.4%)
			18m – 2.5y	39	
			2.5-3.5y	3898	
			>3.5y	139	
			No 2nd surv	**5341**	
AA	**2545**	**12.3**	<18m	627	442 no adenoma (31.0%) 748 NAA (52.5%) **222 AA (15.6%)** 9 cancer (0.6%)
			18m – 2.5y	64	
			2.5-3.5y	697	
			>3.5y	36	
			No 2nd surv	**1120**	
Cancer	102*	0.5			
TOTAL	20722	99.9			

Table 20

* Note date of diagnosis of cancer was within 3m of 1st surveillance in 92 cases, >3m later in 9 cases and >3m before in 1 case.

Summary and discussion

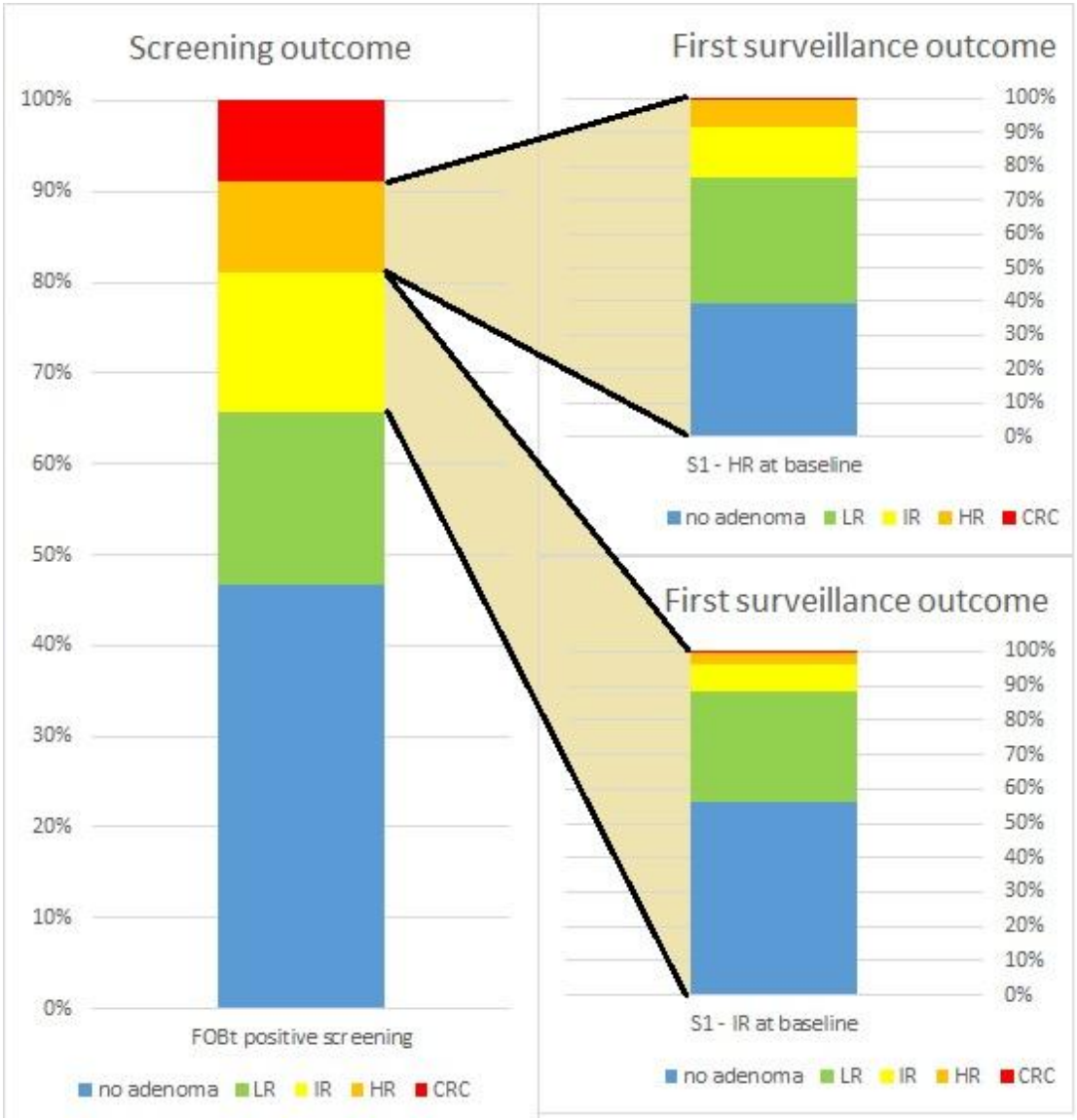

Figure 7 - Outcome of screening and 1st surveillance

The outcomes of FOBt positive screening and first surveillance are presented for comparison in Figure 7 - Outcome of screening and 1st surveillanceFigure 7 above. This figure illustrates that more advanced neoplasia is detected at screening than at first post-polypectomy surveillance.

In both the HR and IR groups, CRC was diagnosed in a low proportion of surveillance episodes (≤0.5%), and the large majority of surveillance episodes found no adenoma or low risk findings.

The key figures presented above show that advanced adenomas are detected at first surveillance in **8.0**% of individuals categorised as intermediate risk at baseline screening, and in **12.3**% of those in the high risk category. This difference was statistically significant with a p-value of 0.000.

It is remarkable that the large majority of surveillance was performed on time, both at first and second surveillance. This indicates the robust system of recall for surveillance in the BCSP as well as subjects' engagement with the programme.

Many individuals had not attended second surveillance. It should be noted that the reason for no second surveillance is not assessed here. Reasons for not having attended a second surveillance episode include the surveillance not yet being due by the date of the data extraction from BCSS, and the individual being aged over 74 years before the second surveillance was due and not opting in to continue in the BCSP beyond this age.

The risk group assigned in BCSS at baseline matched the documented polyp findings in 90.3% of cases. Information available from the BCSS data extract

could not explain the reasons for 9.7% of cases having polyp data out of keeping with their risk category. However, the actual surveillance intervals followed suggest that those individuals with polyp findings meeting high risk criteria were usually recalled for surveillance at the high risk interval of one year, even when BCSS showed a risk category of "intermediate risk".

One reason for this scenario is the BCSP rules for surveillance in cases where an adenoma has been resected piecemeal. Where an adenoma is <10mm in size, its resection being piecemeal will not affect the surveillance interval. Where the adenoma resected piecemeal is 10-19mm, there is endoscopist's discretion as to the appropriate interval for next surveillance. In cases of piecemeal resection of an adenoma of ≥20mm, a "high risk" surveillance interval of one year should be used.

Similarly, many cases categorised in BCSS as "high risk" with polyp data in keeping with intermediate risk findings, appear to follow the BCSP protocol stating that piecemeal resection of an adenoma of ≥10mm may influence the risk categorisation. Therefore, it is likely that the largest adenoma being resected piecemeal resulted in categorisation as high risk.

Section 3 – Analyses of individual factors

The following results are reported in two parts: the first considering colorectal cancer as the primary outcome, and the second focusing on advanced adenoma incidence at first surveillance.

Part A

The primary source of the analysed data was the Bowel Cancer Screening System (BCSS). Data were extracted from BCSS on 3/1/2017 and these data were complete up to 14/12/2016. CRCs diagnosed at a Bowel Cancer Screening Programme (BCSP) diagnostic test were documented in BCSS. However, CRCs diagnosed out with the BCSP are not documented on BCSS. In order to ensure inclusion of all CRCs diagnosed in this surveillance cohort, linked data from the National Cancer Registration and Analysis Service (NCRAS) were also obtained. As these NCRAS data were complete to 31/12/2014, the time period for the following analyses is truncated accordingly. As explained in Timing of diagnosis of cancer above, it was an inclusion criteria for these analyses that a surveillance episode be attended by 30/9/2014. Therefore 28,468 individuals were eligible for analysis, of whom 188 were diagnosed with CRC by the end of follow-up.

		Female – 28.4% of total		Male – 71.6% of total		Total
		N	% of F	N	% of M	
TOTAL		8082	100	20386	100	**28468**
Age group	**<65**	3674	45.5	9584	47.0	**13258**
	65-69	3766	46.6	9158	44.9	**12942**
	>69	642	7.9	1644	8.1	**2286**
BMI	**<18.5**	88	1.1	71	0.4	**159**
	18.5 – 24.9	2112	26.1	4090	20.1	**6202**
	25.0 – 29.9	2678	33.1	8467	41.5	**11145**
	30.0 – 39.9	2247	27.8	8037	28.2	**8037**
	≥40.0	327	4.1	409	2.0	**736**
	Unknown	630	7.8	1559	7.7	**2189**
Smoking	**Y**	1130	14.0	3152	15.5	**4282**
	N	4669	57.8	8680	42.6	**13349**
	Ex-smoker	2264	28.0	8472	41.6	**10736**
	Unknown	19	0.2	82	0.4	**101**
Alcohol	**Y**	4838	59.9	16314	80.0	**21152**
	N	3244	40.1	4072	20.0	**7316**

Table 21 - Baseline characteristics, CRC analysis cohort

Screening risk category

Of the total cohort of 28,468 for analysis of CRC, 14,146 (49.7%) were "high risk" at screening and 14,322 (50.3%) "intermediate risk".

Follow-up time

A standard method of reporting outcomes in cohort studies is to consider rates of disease (an "event") in the cohort during a defined period of observation: in this analysis, cases of CRC in the BCSS surveillance cohort up to 30/9/2014. The denominator for such a rate is measured in years of observation per person: "person-years".

Overall follow-up was 118556 person years at risk. Mean time at risk was 4.16 years and the median 4.12 years. Maximum time at risk was 8.13 years, in keeping with the time from BCSP roll-out in 2006 to the end of CRC follow-up of 30/9/2014.

Overall in the CRC analysis group, the rate of CRC per 100,000 person years was 158.6 (95% confidence intervals: 137.5 – 182.9) with 188 individuals diagnosed with CRC. The following person-years figures are rounded up to whole numbers.

By risk group

For "intermediate risk" screening subjects, 66,356 person-years, with 82 CRCs (rate: 123.6 CRCs per 100,000 person-years) [95% confidence intervals: 99.5 – 153.4].

For "high risk" screening subjects, 52,200 person-years, with 106 CRCs (rate: 203.1 CRCs per 100,000 person-years) [95% confidence intervals: 167.9 – 245.6].

The person-years of follow-up for analysis in both groups is sufficient for conclusions to be drawn on CRC incidence in the medium term, but not to assess enduring long-term effects of polypectomy or surveillance.

By risk group and gender

Male intermediate risk: 43,927 person-years, 59 CRCs (rate: 134.3 CRCs per 100,000 person-years) [95% confidence intervals: 104.1 – 173.4].

Female intermediate risk: 22,430 person-years, 23 CRCs (rate: 102.5 CRCs per 100,000 person-years) [95% confidence intervals: 68.1 – 154.3].

Male high risk: 40,345 person-years, 75 CRCs (rate: 185.9 CRCs per 100,000 person-years) [95% confidence intervals: 148.2 – 233.1].

Female high risk: 11,855 person-years, 31 CRCs (rate: 261.5 CRCs per 100,000 person-years) [95% confidence intervals: 183.9 – 371.8].

Person-years follow-up in intermediate risk males is almost twice that for intermediate risk females, in keeping with the male preponderance in the analysed population. The gender difference seen in the high risk group is greater still, with males followed for more than three times greater person-years compared to high risk females.

By risk group and age group (at screening)

Intermediate risk aged <65: 32,238 person-years, 27 CRCs (rate: 83.8 CRCs per 100,000 person-years) [95% confidence intervals: 57.4 – 122.1].

Intermediate risk aged 65-69: 31,181 person-years, 45 CRCs (rate: 144.3 CRCs per 100,000 person-years) [95% confidence intervals: 107.8 – 193.3].

Intermediate risk aged >69: 2,937 person-years, 10 CRCs (rate: 340.5 CRCs per 100,000 person-years) [95% confidence intervals: 183.2 – 632.9].

High risk aged <65: 22,842 person-years, 46 CRCs (rate: 201.4 CRCs per 100,000 person-years) [95% confidence intervals: 150.8 – 268.9].

High risk aged 65-69: 24,905 person-years, 47 CRCs (rate: 188.7 CRCs per 100,000 person-years) [95% confidence intervals: 141.8 – 251.2].

High risk aged >69: 4,453 person-years, 13 CRCs (rate: 291.9 CRCs per 100,000 person-years) [95% confidence intervals: 169.5 – 502.8].

The significantly lower follow-up time in the oldest age group of individuals aged over 69 at screening is explained by both the smaller number of subjects in this age group and the shorter remaining time within the BCSP age eligibility. It must be noted that the age used in this analysis is age at screening episode. That is, the age at which the subject *entered* surveillance.

Log rank tests

Survival curves (such as Kaplan-Meier) can be used to graph the survival of different groups. "Survival" can, in the context of these CRC analyses, be

defined as CRC-free survival: that is, neither CRC diagnosis nor death occurring by the end of the available follow-up time. In this analysis, there are very few CRC diagnoses in a large cohort. Therefore, the Kaplan-Meier curve appears flat and so cannot be used effectively to compare groups within this cohort. In general, a limitation of survival curves is that the difference in survival between groups varies with time across the follow-up period. A log rank test compares survival between groups across the whole follow-up period. The log rank test is used to test the null hypothesis that there is no difference in survival between groups.

The log rank test is based on the same assumptions as a Kaplan-Meier survival curve: that censoring is not due to differential prognosis between groups or at different time points of entry to the analysis, and that events did occur at the time point specified. It is reasonable to accept these assumptions for the purpose of these analyses in that the dates of events are based on the most accurate data available. With regards to differential prognosis in different groups, it could be argued that age and gender influence different life expectancy. For example, a female undergoing screening (and so entering analysis) at age 60 would be expected to have a longer life expectancy than a male entering analysis at age 73. Other factors documented in this dataset such as BMI, smoking history, alcohol intake, and ASA grade[6] also influence life

[6] The ASA physical status classification system was designed to assess the fitness of patients before surgery. Developed in 1963 by the American Society of Anesthesiologists (ASA), the classification has five categories as follows:
1. Healthy

expectancy, as do factors not available for analysis such as social deprivation and multi-morbidity. It was assumed for these analyses that these factors were similar across subgroups.

Log rank tests were used to assess observed versus expected CRC cases within the dataset. Note that in this context, "expected" refers internally to the data available and not to national rates of colorectal cancer.

The results of the individual log rank tests are not presented here as these results mirrored those of the Cox analyses presented below. As such, the log rank tests served to confirm the findings of the Cox analyses.

Cox proportional hazards regression analysis

The Cox proportional hazard model is one of the most common methods used in time to event analyses. The model is based on several assumptions, one of which concerns tied events. Tied events could be considered relatively unusual when using exact dates (as a tie would require the same number of days to the event). However, the BCSP is highly effective in recalling individuals for surveillance on time at either one or three years. Therefore, the dates of examination at which a CRC could be diagnosed are often at these regular

2. Mild systemic disease
3. Severe systemic disease
4. Severe systemic disease that is a constant threat to life
5. Moribund

intervals. A number of methods can be used to handle tied events. Stata® uses the Breslow method as standard. This method is accurate when the number of events is small and the number of individuals at risk large, as is the case for CRCs in this large cohort.

The following univariable Cox regression analyses were performed using the Breslow method for ties. In each case, the reference group is shown in the results table with a hazard ratio of 1.

Person factors

Age group at screening

	Hazard Ratio for CRC to end of follow-up	**Standard error**	**P value**	**95% confidence interval**	
<65 (n=13258)	1				
65-69 (n=12924)	1.26	0.198	0.135	0.930	1.719
>69 (n=2286)	2.31	0.554	0.000	1.443	3.694

Table 22 - HR for age

Overall p-value = 0.002

Taking the youngest <65 age group as the reference, the hazard ratio increases with age group. Overall, this difference was statistically significant. However, the hazard ratio of 1.26 for the 65-69 age group was not found be statistically significant with a p-value of 0.135 and 95% confidence intervals crossing one.

Gender

	Hazard Ratio for CRC to end of follow-up	Standard error	P value	95% confidence interval	
Female (n=8082)	1				
Male (n=20386)	1.01	0.163	0.944	0.737	1.387

Table 23 - HR for gender

Gender did not have any statistically significant effect on CRC incidence in this analysis despite male gender being a risk for CRC in the general population.

Reported alcohol intake

	Hazard Ratio for CRC to end of follow-up	Standard error	P value	95% confidence interval	
No alcohol consumption reported (n=7316)	1				
Alcohol consumption reported (n=21152)	0.68	0.106	0.014	0.506	0.927

Table 24 - HR for alcohol

Alcohol consumption appears to be associated with a lower likelihood of CRC with a p-value suggesting statistical significance. However, as noted above, the relatively low p-value is likely to be due to the large sample size.

Reported smoking status

	Hazard Ratio for CRC to end of follow-up	Standard error	P value	95% confidence interval	
Non-smoker (n=13349)	1				
Ex-smoker (n=10736)	1.15	0.183	0.368	0.845	1.57
Current smoker (n=4282)	1.11	0.243	0.630	0.724	1.705
Unknown (n=101)	Excluded from Cox regression analysis				

Table 25 - Smoking status

Overall p-value = 0.365

Smoking status had no statistically significant impact on CRC incidence in this cohort.

BMI

BMI	Hazard Ratio for CRC to end of follow-up	Standard error	P value	95% confidence interval	
<18.5 (n=159) *Underweight*	0.90	0.909	0.917	0.124	6.521
18.5 – 24.9 (n=6202) *Healthy weight*	1				
25.0 – 29.9 (n=11145) *Overweight*	0.68	0.134	0.052	0.465	1.004
30.0 – 39.9 (n=8037) *Obese*	0.98	0.192	0.924	0.669	1.440
≥40.0 (n=736) *Severely obese*	1.32	0.534	0.495	0.596	2.916
Unknown (n=2189)	Excluded from Cox regression analysis				

Table 26 - BMI

Overall p-value = 0.954

Although the hazard ratio of 0.68 suggested a lower risk of CRC in overweight individuals (BMI of 25.0 – 29.9) compared to those with a healthy weight (BMI 18.5 – 24.9), this was not found to be statistically significant with a p-value of 0.052, and 95% confidence interval crossing one.

ASA grade

The ASA physical status classification system was designed to assess the fitness of patients before surgery. Developed in 1963 by the American Society of Anesthesiologists (ASA), the classification has five categories as follows:

1. Healthy
2. Mild systemic disease
3. Severe systemic disease
4. Severe systemic disease that is a constant threat to life
5. Moribund.

	Hazard Ratio for CRC to end of follow-up	**Standard error**	**P value**	**95% confidence interval**	
Grade 1 (n=11268)	1				
Grade 2 (n=15003)	1.11	0.173	0.516	0.815	1.505
Grade 3-5 (n=1699)	1.79	0.472	0.028	1.065	3.000

Table 27 – ASA grade

Overall p-value = 0.080

Taking ASA grade 1 as the standard, an ASA grade of 3, 4, or 5 showed a hazard ratio of 1.79 which was statistically significant with the 95% confidence interval not crossing one. However, this result must be viewed in the context of a very large cohort where 93.9% were ASA grade 1 or 2. In view of this, a p-value of 0.028 and lower bound of the 95% confidence interval of 1.065 emphasise the importance of interpreting this result with caution.

Polyp factors

BCSS risk category

	Hazard Ratio for CRC to end of follow-up	Standard error	P value	95% confidence interval	
Intermediate risk (n=14322)	1				
High risk (n=14146)	1.68	0.248	0.000	1.257	2.245

Table 28 - high risk

In keeping with the log rank test, there were a larger than expected number of CRCs in the high risk screening group and this difference was statistically significant. The 95% confidence interval does not cross one.

Any AA at screening

AA at baseline	Hazard Ratio for CRC to end of follow-up	Standard error	P value	95% confidence interval	
No (n=2295)	1				
Yes (n=26173)	0.747	0.181	0.229	0.465	1.201

Table 29 - AA at baseline

91.9% of the CRC analysis cohort had at least one AA at baseline. There was no statistically significant effect of this factor upon subsequent CRC incidence.

Number of adenomas at baseline

Total adenomas at screening	Hazard Ratio for CRC to end of follow-up	Standard error	P value	95% confidence interval	
1 (n=8191)	1				
2 (n=5321)	1.53	0.336	0.052	0.997	2.357
3 (n=5743)	1.14	0.278	0.600	0.704	1.834
4 (n=3283)	1.53	0.409	0.112	0.905	2.584
5 (n=2242)	1.74	0.525	0.065	0.966	3.146
6 – 9 (n=2883)	2.60	0.629	0.000	1.615	4.172
≥10 (n=805)	3.82	1.253	0.000	2.010	7.266

Table 30 - multiplicity

Overall p-value = 0.000

The hazard ratio increased with increasing number of adenomas at baseline, with statistical significance being reached for individuals with greater than five adenomas.

Size of largest adenoma at baseline

Largest adenoma	Hazard Ratio for CRC to end of follow-up	Standard error	P value	95% confidence interval	
<6mm (n=1411)	1.47	0.447	0.209	0.807	2.663
6-9mm (n=1901)	1.23	0.364	0.482	0.690	2.196
10-14mm (n=9786)	1				
15-19mm (n=7136)	0.96	0.187	0.817	0.652	1.401
20-29mm (n=5711)	1.03	0.209	0.900	0.688	1.529
30-39mm (n=1492)	0.86	0.322	0.684	0.411	1.791
≥40mm (n=1001)	1.03	0.442	0.938	0.448	2.389
Unknown (n=30)	Excluded from Cox regression analysis				

Table 31 - size of largest adenoma

Overall p-value = 0.87

There was no statistically significant effect of adenoma size seen on CRC incidence.

Number and size of adenomas at baseline

Baseline findings	Hazard Ratio for CRC to end of follow-up	Standard error	P value	95% confidence interval	
1 adenoma, ≥10mm (n=8180)	1				
2 adenomas, at least one ≥10mm (n=5317)	1.53	0.336	0.052	0.996	2.356
3 adenomas <10mm (n=1288)	0.94	0.411	0.889	0.400	2.213
3 adenomas, at least one ≥10mm (n=4450)	1.20	0.317	0.481	0.718	2.018
4 adenomas <10mm (n=618)	2.68	1.035	0.010	1.260	5.717
4 adenomas, at least one ≥10mm (n=2661)	1.21	0.384	0.550	0.649	2.254
≥5 adenomas <10mm (n=1406)	2.61	0.831	0.003	1.400	4.874
≥5 adenomas, at least one ≥10mm (n=4518)	2.40	0.521	0.000	1.565	3.671
Missing data (n=30)	Excluded from Cox regression analysis				

Table 32 - size and number of adenomas

Overall p-value = 0.0009

Compared to one large adenoma, there is no significant effect on CRC incidence for two or three adenomas. Four adenomas shows statistical significance in the

group with no large adenoma. However, this group is small (n=618). There is a statistically significant increase in risk of CRC seen in those with at least five adenomas at baseline, and a similar hazard ratio of around 2.5 is seen with or without an adenoma ≥10mm.

High grade dysplasia at screening

HGD at baseline	Hazard Ratio for CRC to end of follow-up	Standard error	P value	95% confidence interval	
No (n=23348)	1				
Yes (n=4950)	1.21	0.217	0.298	0.849	1.719
Unknown (n=170)	Excluded from Cox regression analysis				

Table 33 - HGD

No significant effect of high grade dysplasia was seen.

Highest villous architecture at screening

Highest villous at baseline	Hazard Ratio for CRC to end of follow-up	Standard error	P value	95% confidence interval	
TA (n=10230)	1				
TVA (n=16645)	1.01	0.156	0.950	0.746	1.367
VA (n=1435)	1.07	0.361	0.852	0.548	2.069
unknown (n=158)	Excluded from Cox regression analysis				

Table 34 - villous

Overall p-value = 0.885

No significant effect of villous architecture was seen on CRC incidence.

Proximal adenoma at screening (proximal to splenic flexure)

Any proximal adenoma at baseline	Hazard Ratio for CRC to end of follow-up	Standard error	P value	95% confidence interval	
No (n=16602)	1				
Yes (n=11866)	1.60	0.233	0.001	1.199	2.127

Table 35 - proximal adenoma

There was a statistically significant increase in cases of CRC among individuals with at least one adenoma proximal to the splenic flexure at screening, compared to those with no adenoma proximal to the splenic flexure.

Procedure factors

Time interval to first surveillance (intermediate risk group)

Actual surveillance interval	Hazard Ratio for CRC to end of follow-up	Standard error	P value	95% confidence interval	
<2.5y (n=1205)	3.88	1.184	0.000	2.134	7.059
2.5 – 3.5 y (n=12648)	1				
>3.5y (n=469)	0.37	0.372	0.322	0.051	2.658

Table 36 - time to first surveillance (IR)

Delayed first surveillance in the intermediate risk group had no significant effect on CRC incidence. There was a statistically significant increase in CRC incidence seen in those attending early for first surveillance. As detailed in

Summary and discussion above, this result appears to reflect this subgroup being deemed to have higher risk factors at baseline and being recalled for surveillance at a one year interval (for example, an adenoma of ≥20mm).

Time interval to first surveillance (high risk group)

Actual surveillance interval	Hazard Ratio for CRC to end of follow-up	Standard error	P value	95% confidence interval	
<11m (n=79)	3.15	2.248	0.109	0.775	12.762
11 – 18m (n=12979)	1				
>18m (n=1088)	0.75	0.292	0.455	0.346	1.609

Table 37 - time to first surveillance (HR)

In the high risk screening group, no statistically significant effect of surveillance interval was seen on CRC incidence.

Suboptimal procedure at baseline (caecum not reached or "poor" bowel prep)

Suboptimal screening	Hazard Ratio for CRC to end of follow-up	Standard error	P value	95% confidence interval	
No (n=27671)					
Yes (n=797)	1.03	0.426	0.948	0.456	2.318

Table 38 - suboptimal screening

In the small group with a suboptimal baseline screening episode, no significant difference was seen in CRC incidence compared to the majority with no marker for suboptimal quality.

Piecemeal resection of any adenoma at baseline

Any piecemeal resection	Hazard Ratio for CRC to end of follow-up	Standard error	P value	95% confidence interval	
No (n=25686)	1				
Yes (n=2782)	1.39	0.379	0.230	0.812	2.371

Table 39 - piecemeal resection

Piecemeal resection of an adenoma occurred at baseline screening on less than 10% of the CRC analysis cohort. There was no significant effect seen on CRC incidence.

Year of screening episode

Year screened	Hazard Ratio for CRC to end of follow-up	Standard error	P value	95% confidence interval	
2006 – 2008 (n=4962)	1				
2009 – 2010 (n=12543)	0.78	0.147	0.187	0.538	1.129
2011 onwards (n=10963)	1.18	0.244	0.428	0.785	1.769

Table 40 - Year screened

A number of changes in the practices and procedures of the BCSP took place during the study period. For example, the use of the binomial "resected" field in the BCSS definition of an adenoma was introduced in 2011. The field "secondary piece" was introduced in 2008 in order to denote the same polyp being documented at a different diagnostic test during the same episode. Due

to the potential for changes in procedures and documentation to impact upon risk categorisation and so influence the results of these analyses, the above year screened variable was created. There was no statistically significant effect on CRC incidence seen.

Multivariable model

The above univariable results informed the creation of a multivariable model based on Cox regression analysis. The methods described in Univariable & Multivariable analyses were followed in order to assess for multicollinearity, proportionality of hazards, and goodness of fit of the proposed model.

The final model is presented below.

n=28468		**Hazard Ratio for CRC to end of follow-up**	**Standard error**	**P value**	**95% confidence interval**	
Age at screening	<65	1				
	65-69	1.23	0.193	0.188	0.904	1.673
	>69	2.09	0.504	0.002	1.300	3.351
Number of adenomas	1	1				
	2	1.52	0.334	0.055	0.990	2.342
	3	1.11	0.270	0.683	0.684	1.784
	4	1.48	0.397	0.142	0.876	2.504
	5	1.67	0.503	0.091	0.922	3.010
	6-9	2.45	0.597	0.000	1.524	3.953
	≥10	3.58	1.177	0.000	1.880	6.821

Table 41 - Statistical model

Overall p-value = 0.0000

A p-value of ≤0.05 was reached only for ≥6 adenomas and age at screening >69 years. For both variables at these thresholds, the hazard ratio was greater than 2.

Measures of collinearity indicated no significant collinearity with a VIF of 1.01 for both variables included in the multivariable model. Test of proportional-hazards (using Schoenfeld residuals) showed a global chi-squared value of 12.47 and p-value of 0.131 (and all individual p-values were >0.05). These measures indicate that the proportionality of hazards assumption, on which Cox analysis relies, has not been violated.

Summary & conclusions for CRC analyses

Factors which are known to influence the risk of CRC in the general population were included in the above analyses: gender, BMI, smoking history, and alcohol intake. But importantly, these factors have not been shown to be associated with missed lesions at colonoscopy: the likely explanation for the CRC cases in these analyses.

The definition of post-colonoscopy colorectal cancer (PCCRC) is a CRC detected up to thirty-six months after a colonoscopy at which no CRC was detected. Based on understanding of the adenoma-carcinoma sequence, this definition assumes that all PCCRCs are due to a lesion present at the time of

the previous colonoscopy. The reason for this pre-existing lesion not being fully resected may be that the lesion was not detected, was not resected, or was incompletely resected. It is considered highly improbable that a CRC could develop from normal colorectal mucosa within a time period of three years or less.

As anticipated, older age conferred higher risk of CRC in this analysis cohort. Across the entire cohort, there was no significant difference in CRC incidence based on gender. It would be expected that a higher CRC incidence would be seen in males compared to females.

Other factors known to be associated with increased CRC incidence were, in this analysis, found not to be significant, namely BMI and smoking history. There was in fact a small reduction in CRC incidence in individuals who reported alcohol intake compared to those who did not, and this difference was statistically significant. However, this result must be viewed in the context of a small difference in a very large analysis cohort and so no clinically relevant conclusion can be drawn. Moreover, statistical significance was not seen for alcohol intake in multivariable analysis.

In summary, the factors known to increase CRC risk in the general population do not, in general, confer increased risk in this cohort with the exception of older age. This observation supports the concept that colorectal dysplasia is

more likely in individuals with these risk factors, but that progression along the adenoma-carcinoma sequence may not be driven by these same factors.

Other created analysis variables were also assessed with reference to CRC incidence. These were "Multi_Tests": indicating more than one diagnostic test occurring during the screening episode, "No_Col": indicating that no colonoscopy had occurred during the screening episode, and "Col_incomplete": indicating that a complete colonoscopy had not been performed within the screening episode. The presence of these scenarios during a screening episode could be expected to increase CRC risk. The lack of any colonoscopy or lack of a complete colonoscopy increases the rate of CRC subsequently diagnosed. The presence of multiple tests indicates the likelihood of multiple or complex polyps requiring repeat examinations to achieve clearance of all adenomatous tissue.

As anticipated, an incomplete endoscopic examination of the colon was associated with a higher CRC incidence. However, the presence of multiple tests or absence of a colonoscopy in the screening episode were not associated with a statistically significant difference in CRC incidence. The small numbers of individuals in these subgroups limits the conclusions which can be drawn. The small number in these subgroups are also a testament to the high quality of the BCSP and high success rate in achieving complete colonic examination.

The above results show:

1. No significant difference in CRC incidence between males and females in this surveillance cohort.
2. A higher incidence of CRC in the older age group.
3. A higher incidence of CRC in individuals found to have a very large number of adenomas (≥6) at baseline screening.

Overall, the number of CRC diagnoses in this cohort is small. This supports the hypothesis that index screening colonoscopy and polypectomy is effective in protecting against CRC. It would be anticipated that the incidence of CRC diagnosis at surveillance would be low given the previous colonoscopy and polypectomy within the previous three years. It must be remembered that a diagnosis of cancer within three years of a previous colonoscopy is likely to represent a lesion missed at the previous colonoscopy and not the development of a new lesion since the previous colonoscopy. This three year time period is used in the definition of a "post-colonoscopy colorectal cancer" (PCCRC) and is also the longer of the two surveillance intervals followed in the BCSP. Therefore, by definition, a CRC diagnosed at surveillance in the BCSP would be assumed to have arisen from a missed lesion, a PCCRC, and cannot be defined as the development of a CRC from normal mucosa since the previous colonoscopy. However, it must be borne in mind that some cancers may not follow the conventional adenoma-carcinoma sequence, for example serrated lesions, and may develop more rapidly.

Of greater importance for the effectiveness of surveillance is the advanced adenoma incidence as this presents an opportunity for CRC prevention through polypectomy. This outcome will be the focus of the following section of this thesis.

Part B

The primary source of the analysed data was the Bowel Cancer Screening System (BCSS). Data were extracted from BCSS on 3/1/2017 and these data were largely complete up to that date. Episodes occurring close to the date of data extraction may have incomplete pathology results. This is due to prospective data entry to BCSS: procedural data are entered at the time of the endoscopic procedure, then associated pathology data are entered some days later when these results are available. As such, episodes were identified as having pathology data missing where the episode occurred after 14/12/2016.

In this analysis, cases of advanced adenoma (AA) were considered an "event". Advanced adenoma was defined by convention as the presence of any one of three factors: diameter ≥10mm, high grade dysplasia, or villous component (≥25%).

Logistic regression analysis

For analyses using AA as the primary outcome, logistic regression analysis was used. This statistical model was developed by David Cox, whose eponymous technique was used for CRC survival analyses earlier in this chapter.

Used in its binary form, logistic regression can be used to model the probability of an outcome based on a dependent variable or variables. Time to event is not taken into account (as it is in Cox survival analyses). In the context of AA at surveillance, this has the effect of excluding the effect of surveillance interval. That is, an AA detected at first surveillance after one year is an event ("1"), as is an AA detected at first surveillance after three years, or at any other time point. This feature of logistic regression must be borne in mind when interpreting the following results. However, this analysis approach is in keeping with our understanding of the adenoma-carcinoma sequence and its slow progression. It is therefore a reasonable assumption that findings at first surveillance would be similar at either a one or three year interval.

The alternative strategy of performing time to event analysis (such as Cox regression) would have the effect of assigning a three year "disease free" period to all those attending first surveillance at that interval and just one year of "disease free" follow up for those attending on a high risk category surveillance interval. As a primary aim of this study was to investigate the accuracy of current risk categorisation in predicting future colonoscopy findings, it was essential to analyse both high and intermediate risk subjects together. Logistic regression has allowed this combined analysis to be performed.

Outcome of any advanced adenoma at first surveillance episode

Numbers, percentages, and univariable odds ratios

The following analyses use an outcome, ("event") of any AA found at the first surveillance episode attended by that individual.

Person factors

Any AA at 1st surveillance episode by age at screening episode

Age group	No AA at 1st surv	Any AA at 1st surv	Total	Odds ratio	p
<65	17896	1908 (9.6%)	19804	1	
65-69	16624	1980 (10.6%)	18604	1.12	0.001
>69	4032	511 (11.3%)	4543	1.19	0.001
TOTAL	38552	4399	42951		

Table 42 - Age

Overall p-value = 0.000

AA at first surveillance increased with age at screening and the difference was statistically significant.

Any AA at 1st surveillance episode by gender

Gender	No AA at 1st surv	Any AA at 1st surv	Total	Odds ratio	p
Female	11571	1092 (8.6%)	12663	1	
Male	26981	3307 (10.9%)	30288	1.30	0.000
TOTAL	38552	4399 **(10.2%)**	42951		

Table 43 - Gender

Males were found to have AA at first surveillance more often than females with a statistically significant odds ratio of 1.3.

Any AA at 1st surveillance episode by alcohol intake

Reported alcohol intake	No AA at 1st surv	Any AA at 1st surv	Total	Odds ratio	p
None	10309	1079 (9.5%)	11388	1	
≤14 units/week	15349	1656 (9.7%)	17005	1.03	0.461
≥15 units/week	12894	1664 (11.4%)	14558	1.23	0.000
TOTAL	38552	4399	42951		

Table 44 - Alcohol

Overall p-value = 0.0000

The rate of AA at first surveillance was higher in individuals stating that they consumed more than the recommended maximum of fourteen units of alcohol per week.

Any AA at 1st surveillance episode by smoking status

Reported smoking status	No AA at 1st surv	Any AA at 1st surv	Total	Odds ratio	p
Non-smoker	18494	1930 (9.5%)	20424	1	
Ex-smoker	14448	1689 (10.5%)	16137	1.12	0.001
Current smoker	5485	766 (12.3%)	6251	1.34	0.000
Unknown	125	14 (10.1%)	139	Excluded from logistic regression	
TOTAL	38552	4399	42951		

Table 45 - Smoking

Overall p-value = 0.000

AA at first surveillance varied with smoking status such that non-smokers were lowest risk and current smokers highest risk.

Any AA at 1st surveillance episode by BMI

BMI	No AA at 1st surv	Any AA at 1st surv	Total	Odds ratio	p
<18.5	206	30 (12.7%)	236	1.28	0.207
18.5 – 24.9	8319	943 (10.2%)	9262	1	
25.0 – 29.9	15280	1668 (9.8%)	16948	0.96	0.380
30.0 – 39.9	10956	1314 (10.7%)	12270	1.05	0.211
≥40.0	1071	122 (10.2%)	1193	1.00	0.961
unknown	2720	322 (10.6%)	3042	Excluded from logistic regression	
TOTAL	38552	4399	42951		

Table 46 - BMI

Overall p-value = 0.383

BMI had no statistically significant effect on AA at first surveillance.

Any AA at 1st surveillance episode by ASA grade

ASA grade	No AA at 1st surv	Any AA at 1st surv	Total	Odds ratio	p
1	14807	1516 (9.3%)	16323	1	
2	20977	2494 (10.6%)	23471	1.16	0.000
3-5	2145	340 (13.7%)	2485	1.55	0.000
Unknown	623	49 (7.3%)	672	Excluded from logistic regression	
TOTAL	38552	4399	42951		

Table 47 - ASA grade

Overall p-value = 0.0000

AA at first surveillance increased in line with ASA grade and this effect was found to be statistically significant.

Polyp factors

Any AA at 1st surveillance episode by BCSS risk category

BCSS risk category	No AA at 1st surv	Any AA at 1st surv	Total	Odds ratio	p
Intermediate	20475	1827 (8.2%)	22302	1	
High	18077	2572 (12.5%)	20649	1.59	0.000
TOTAL	38552	4399 **(10.2%)**	42951		

Table 48 - Risk category

BCSS risk category had a statistically significant effect on AA at first surveillance.

Any AA at 1st surveillance episode by any AA at screening episode

AA at screening	No AA at 1st surv	Any AA at 1st surv	Total	Odds ratio	p
0	4003	426 **(9.6%)**	4429	1	
≥1	34549	3973 **(10.3%)**	38522	1.08	0.149
TOTAL	38552	4399 **(10.2%)**	42951		

Table 49 - AA at baseline

The presence of any advanced adenoma at screening had no significant effect on the likelihood of finding further AA at first surveillance.

Any AA at 1st surveillance episode by total number of adenomas at screening episode

Total adenomas at screening	No AA at 1st surv	Any AA at 1st surv	Total	Odds ratio	p
1	11589	778 (6.3%)	12367	1	
2	7190	792 (9.9%)	7982	1.64	0.000
3	7687	838 (9.8%)	8525	1.62	0.000
4	4177	571 (12.0%)	4748	2.04	0.000
5	2819	455 (13.9%)	3274	2.40	0.000
6-9	3612	674 (15.7%)	4286	2.78	0.000
>9	977	253 (20.6%)	1230	3.86	0.000
Missing data	501	38 (7.1%)	539	Excluded from logistic regression	
TOTAL	38552	4399	42951		

Table 50 - multiplicity

Overall p-value = 0.0000

Individuals possessing only one adenoma at screening was the largest group, comprising 12,367 individuals. It must be noted that these solitary adenomas must have measured at least 10mm in size in order for that screening episode to be classed at intermediate risk and for surveillance to be advised. This group had the lowest rate of AA at first surveillance at only 6.3%. The proportion of individuals found to have any AA at first surveillance increased in a linear fashion with increasing number of adenomas at baseline. Odds ratios also followed this linear increase and were highly statistically significant with p-value of 0.000.

Any AA at 1st surveillance episode by size of largest adenoma at screening episode

Largest adenoma at screening	No AA at 1st surv	Any AA at 1st surv	Total	Odds ratio	P
<6mm	2174	237 (9.8%)	2411	1.12	0.127
6-9mm	2754	408 (12.9%)	3162	1.52	0.000
10-14mm	13756	1339 (8.9%)	15095	1	
15-19mm	9186	955 (9.4%)	10141	1.07	0.139
20-29mm	7082	883 (11.1%)	7965	1.28	0.000
30-39mm	1817	278 (13.3%)	2095	1.57	0.000
>39mm	1256	257 (17.0%)	1513	2.10	0.000
Missing	527	42 (7.4%)	569	Excluded from logistic regression	
TOTAL	38552	4399 (10.2%)	42951		

Table 51 - largest adenoma

Overall p-value = 0.0000

There was a statistically significant effect of size of largest adenoma with an odds ratio of greater than 2 for size of greater than 39mm.

Any AA at 1st surveillance episode by number and size of adenomas at baseline

Adenomas at screening	No AA at 1st surv	Any AA at 1st surv	Total	Odds ratio	p
1 adenoma, ≥10mm	11580	776 (6.3%)	12356	1	
2 adenomas, at least one ≥10mm	7186	792 (9.9%)	7978	1.64	0.000
3 adenomas <10mm	1984	230 (10.4%)	2214	1.73	0.000
3 adenomas, at least one ≥10mm	5698	608 (9.6%)	6306	1.59	0.000
4 adenomas <10mm	943	120 (11.3%)	1063	1.90	0.000
4 adenomas, at least one ≥10mm	3232	449 (12.2%)	3681	2.07	0.000
≥5 adenomas <10mm	2001	295 (12.9%)	2296	2.20	0.000
≥5 adenomas, at least one ≥10mm	5401	1087 (16.8%)	6488	3.00	0.000
Missing data	527	42 (7.4%)	569	Excluded from logistic regression	
TOTAL	38552	4399	42951		

Table 52 - number and size of adenomas

Overall p-value = 0.0000

There is a linear increase in the likelihood of AA at first surveillance by the number of adenomas at screening. In the case of four or more adenomas, the presence of a large adenoma further increases this risk.

Any AA at 1st surveillance episode by maximum dysplasia in any adenoma at screening episode

Maximum dysplasia any adenoma at screening	No AA at 1st surv	Any AA at 1st surv	Total	Odds ratio	p
Low	31607	3579 (10.2%	35186	1	
High	6258	769 (10.9%)	7027	1.09	0.052
Missing	687	51 (6.9%)	738	Excluded from logistic regression	
TOTAL	38552	4399	42951		

Table 53 - HGD

HGD at screening did not have any statistically significant effect upon AA at first surveillance.

Any AA at 1st surveillance episode by highest villous architecture in any adenoma at screening

Highest villous architecture	No AA at 1st surv	Any AA at 1st surv	Total	Odds ratio	p
TA	14170	1284 (8.3%)	15454	1	
TVA	21999	2771 (11.2%)	24770	1.39	0.000
VA	1710	292 (14.6%)	2002	1.88	0.000
Unknown	673	52 (7.2%)	725	Excluded from logistic regression	
TOTAL	38552	4399	42951		

Table 54 - villous

Overall p-value = 0.000

Increasing villous architecture at baseline increased the chance of AA at first surveillance and this difference was statistically significant. Interestingly, most subjects (62.3%) had villous architecture (at least TVA) at baseline, despite the fact that most adenomas are tubular adenomas. This may reflect the higher

adenoma burden in those qualifying for and attending surveillance: particularly the fact that most of this cohort had at least one large (≥10mm) adenoma at screening, as villous architecture tends to increase with adenoma size.

Any AA at 1st surveillance episode by presence of either TVA *or* VA at screening

Any TVA OR VA	**No AA at 1st surv**	**Any AA at 1st surv**	**Total**	**Odds ratio**	**p**
0	14778	1330 (8.3%)	16108	1	
1	23709	3063 (11.4%)	26772	1.44	0.000
TOTAL	38487	4393	42880		

Table 55 - any villous

Simplifying the analysis of villous architecture to a binary variable also shows a statistically significant difference in AA at first surveillance. The overall percentage AA and the odds ratio more closely reflect the figures seen for TVA above due to the large size of that subgroup (57.7% of the total cohort).

Any AA at 1st surveillance episode by presence of any proximal adenoma at screening (proximal to splenic flexure)

Any proximal adenoma	No AA at 1st surv	Any AA at 1st surv	Total	Odds ratio	p
0	22812	2039 (8.2%)	24851	1	
1	15675	2354 (13.1%)	18029	1.68	0.000
TOTAL	38487	4393	42880		

Table 56 - proximal adenoma

The presence of a proximal adenoma compared to none increased the risk of AA being detected at first surveillance.

Procedure factors

Any AA at 1st surveillance episode by time interval to first surveillance in intermediate risk screening group

1st surv interval	No AA at 1st surv	Any AA at 1st surv	Total	Odds ratio	P
<2.5y	1288	228 (15.0%)	1516	2.13	0.000
2.5y-3.5y	18343	1527 (7.7%)	19870	1	
>3.5y	844	72 (7.9%)	916	1.02	0.846
TOTAL	20475	1827 (8.2%)	22302		

Table 57 - interval (IR)

In the intermediate risk category, those attending first surveillance at least six months late had no increased risk of AA. Those attending first surveillance early were more likely to have AA and this difference was statistically significant. However, as detailed in "Intermediate risk at screening", this result is likely to reflect this subgroup being deemed to have higher risk factors at baseline and being recalled for surveillance at a one year interval (for example, an adenoma of ≥20mm).

Any AA at 1st surveillance episode by time interval to first surveillance in high risk screening group

1st surv interval	No AA at 1st surv	Any AA at 1st surv	Total	Odds ratio	p
<11m	89	11 (11.0%)	100	0.88	0.677
11-18m	16649	2351 (12.4%)	19000	1	
>18m	1338	210 (13.6%)	1548	1.11	0.172
TOTAL	18076	2572 (12.5%)	20648		

Table 58 - interval (HR)

Of individuals in the high risk category, there was no statistically significant difference in AA based on timing of first surveillance.

Any AA at 1st surveillance episode by suboptimal quality at baseline

Suboptimal screening	No AA at 1st surv	Any AA at 1st surv	Total	Odds ratio	p
0	37562	4249 (10.2%)	41811	1	
1	990	150 (13.2%)	1140	1.34	0.001
TOTAL	38487	4393	42880		

Table 59 - suboptimal screening

A variable was created to denote a suboptimal quality screening episode, defined as either "poor" bowel preparation or maximum extent distal to the caecum (i.e. incomplete colonoscopy). The presence of one of these markers of suboptimal quality at screening increased the likelihood of AA at first surveillance. However, the small number of individuals meeting criteria for suboptimal quality must be borne in mind.

Any AA at 1st surveillance episode by piecemeal resection of an adenoma at screening

Piecemeal resection of an adenoma	No AA at 1st surv	Any AA at 1st surv	Total	Odds ratio	p
0	33737	3659 (9.8%)	37396	1	
1	4750	734 (13.4%)	5484	1.42	0.000
TOTAL	38487	4393	42880		

Table 60 - piecemeal resection

The piecemeal resection of any adenoma at screening increased the risk of AA being detected at first surveillance and this was a statistically significant difference on univariate logistic regression analysis.

Any AA at 1st surveillance episode by year of screening episode

Year screened	No AA at 1st surv	Any AA at 1st surv	Total	Odds ratio	p
2006 – 2008	4678	496 (9.6%)	5174	1	
2009 – 2011	18061	2069 (10.3%)	20130	1.08	0.142
2012 onwards	15813	1834 (10.4%)	17647	1.09	0.092
TOTAL	38552	4399	42951		

Table 61 - year screened

As detailed in "Procedure factors", the above analysis of the year of screening episode was performed to assess for any effect of changes in the BCSP over the time period studied.

AA at first surveillance was similar across time periods of the BCSP, indicating no large impact from the changes implemented during the study period.

Multivariable logistic regression for AA at first surveillance

The above univariable analyses informed the following multivariable analyses. It is notable that most variables considered did show a statistically significant effect on the detection of AA at the first surveillance episode. Statistical significance, defined as a p-value of ≤0.05, must be interpreted in the context of this very large analysis cohort. It is therefore perhaps more informative to assess the odds ratio for a particular variable in gauging the importance of that factor in predicting AA.

For consideration of inclusion in the multivariable model, a p-value threshold of ≤0.1 was used and the methods described in "Univariable & Multivariable analyses" were followed in order to assess for multicollinearity, proportionality of hazards, and goodness of fit of the proposed model.

The final model is presented below.

n=41519		Odds Ratio	Standard error	P value	95% confidence interval	
Gender	Male	1.13	0.044	0.001	1.050	1.224
Suboptimal screening	Yes	1.46	0.135	0.000	1.220	1.754
Number of adenomas	1	1				
	2	1.56	0.084	0.000	1.408	1.737
	3	1.58	0.084	0.000	1.425	1.754
	4	1.90	0.113	0.000	1.693	2.137
	5	2.24	0.144	0.000	1.973	2.539
	6-9	2.47	0.144	0.000	2.208	2.774
	≥10	3.03	0.252	0.000	2.578	3.571
Maximum villous architecture	TA	1				
	TVA	1.37	0.050	0.000	1.278	1.473
	VA	1.70	0.121	0.000	1.475	1.953
Non-pedunculated adenoma ≥10mm	Yes	1.38	0.050	0.000	1.288	1.483
Smoking status	Non / ex	1				
	Current	1.16	0.051	0.001	1.065	1.264
Alcohol intake (weekly)	≤14 units	1				
	≥15 units	1.09	0.381	0.010	1.022	1.171
ASA grade	1	1				
	2	1.09	0.038	0.019	1.013	1.162
	3-5	1.33	0.880	0.000	1.167	1.513

Table 62 - statistical model

Overall p-value = 0.0000

The above model is, by statistical measures, the best multivariable model for the variables tested in predicting AA at first surveillance.

Measures of collinearity indicated no significant collinearity with a VIF of <1.1 for all variables included in the multivariable model and a mean VIF of 1.04.

From a perspective of clinical utility, there are a number of included variables which would be unlikely to reliable or acceptable for inclusion in clinical practice. For example, males had a significantly higher rate of AA at first surveillance, but a relatively low odds ratio of 1.13 in the multivariable model. It is unlikely that this would be seen as sufficient evidence to make differing recommendations for males and females. Therefore, there is a clinical rationale for removing gender from the model.

Similarly, lifestyle factors such as smoking status and alcohol intake were found to have statistically significant effects, but with relatively low odds ratios of 1.16 and 1.09 respectively. Again, this may not be sufficient evidence to suggest differing surveillance regimens for individuals reporting they are smokers and / or consume greater than fourteen units of alcohol weekly.

ASA grade of 3-5 was found to significantly increase risk of AA first surveillance compared to ASA grade 1, with an odds ratio of 1.33. However, this presents a clinical dilemma: individuals with greater multi-morbidity have a higher chance of being found to have AA at surveillance. But does this mean this group should have more intensive surveillance? The opposing argument would be that individuals aged greater than 60 years (and therefore in this cohort) with significant medical conditions, are the group least likely to benefit from surveillance. This is because detection and resection of further adenomas

with the aim of reducing CRC incidence takes effect over a long time period: potentially a similar or longer time period than the remaining life expectancy of a patient group with significant multi-morbidity.

On this basis, a reduced model is suggested comprising only those factors likely to be of clinical utility in everyday practice:

n=42226		**Odds Ratio**	**Standard error**	**P value**	**95% confidence interval**	
Suboptimal screening	Yes	1.54	0.141	0.000	1.292	1.847
Number of adenomas	1	1				
	2	1.59	0.084	0.000	1.433	1.764
	3	1.65	0.086	0.000	1.489	1.828
	4	2.01	0.117	0.000	1.789	2.250
	5	2.38	0.151	0.000	2.106	2.698
	6-9	2.66	0.151	0.000	2.377	2.969
	≥10	3.36	0.274	0.000	2.868	3.945
Maximum villous architecture	TA	1				
	TVA	1.35	0.486	0.000	1.261	1.451
	VA	1.66	0.118	0.000	1.446	1.910
Non-pedunculated adenoma ≥10mm	Yes	1.38	0.492	0.000	1.284	1.477

Table 63 - simplified model

Conclusion

This section has considered the factors influencing the detection of advanced adenomas at first surveillance, across both intermediate and high risk groups. It is notable that many person, procedure, and polyp factors were found to have statistical significance in this analysis. A pragmatic approach is advised in applying these findings to clinical practice. As such, a suggested model is presented including a reduced number of these statistically significant factors, namely: suboptimal screening episode, number of adenomas, villous architecture, and the presence of any non-pedunculated adenoma of ≥10mm.

The pattern of risk seen for largest adenoma at baseline is mixed: Table 51 - largest adenoma. This is explained by the cohort being studied: individuals with one or two adenomas at baseline must have at least one adenoma of ≥10mm in order to be classified as at least intermediate risk and so qualify for surveillance. Given the linear relationship presented above for number of adenomas at screening, the lowest risk group is again dominated by those with a single (10-14mm) adenoma at screening. A higher chance of AA at first surveillance in those with only small adenomas seems counterintuitive in view of published literature on adenoma size. However, this finding must be viewed in light of this surveillance cohort being analysed: those with only small adenomas must have at least three adenomas at baseline, while individuals with an adenoma of ≥10mm may have only a single adenoma at baseline.

A key finding presented in this section is presented in Table 52: the lowest incidence of advanced adenoma at first surveillance was in the group with a single adenoma at baseline. By definition, the single adenoma was ≥10mm in size in order to be classified as intermediate risk and so be invited for surveillance. This large subgroup of the surveillance population studied numbered 12356 individuals (28.8% of the total) and were found to have an AA at first surveillance in only 6.3% of cases.

CHAPTER 6 – Discussion

Colorectal cancer can develop below the age of 60 years. However, evidence suggests that adults over the age of 60 are at the highest risk of developing the disease. There is anxiety about a higher risk of cancer in those diagnosed with colorectal adenomas. This is the rationale for post-polypectomy surveillance. It is, however, legitimate to question which individuals should be offered surveillance and at what time interval.

The aims of this thesis were to quantify the risk of developing a cancer for individuals diagnosed with adenomas in the BCSP, and to identify factors conferring higher risk. In order to address these aims, the following objectives were identified. Firstly, a systematic review of the literature was performed to aggregate evidence on advanced adenoma incidence at surveillance following intermediate risk. Secondly, analysis of retrospective data from the English BCSP was performed.

The most important findings of this thesis were that:

1. CRC rates among the surveillance cohort in the BCSP are low.
2. Individuals qualifying as "intermediate risk" by resection of a single adenoma of at least ten millimetres diameter have a particularly low subsequent risk of advanced colorectal neoplasia.

3. The number of adenomas at baseline was seen to be more strongly predictive of surveillance findings than the size of the largest adenoma at baseline.
4. In addition to the current classification using size and number of adenomas, there are additional adenoma factors which modify risk in those individuals attending for post-polypectomy surveillance, such as villous architecture, as well as person factors such as age or gender.

The data analysis focussed on both intermediate and high risk subjects, as defined by current criteria. The primary objectives were to quantify the risk of advanced colorectal neoplasia (ACN) at surveillance in both risk groups, to assess the effect of delayed surveillance on ACN incidence, and to identify factors conferring higher risk of ACN at surveillance for both risk groups.

The systematic review showed evidence from international literature that an extended surveillance interval in the intermediate risk group did not significantly increase incidence of advanced adenomas or cancer. The geographical diversity and large total population were strengths of this review. Limitations included the heterogeneity of study designs and study settings, as well as the majority of included studies being retrospective.

The analysis of BCSP data presented here represents a very large post-polypectomy cohort of intermediate and high risk individuals. The data

analysed is prospectively entered onto the BCSS database, including procedural data being added during the endoscopy and histology data being added when available subsequently. Many data fields in BCSS are compulsory fields and as such there are very few missing data. Data accuracy is monitored by regular audit whereby each Specialist Screening Practitioner (SSP) audits 10% of their data entry on a monthly basis and SSPs are prompted to enter any outstanding histology data. Quality standards are closely monitored in the BCSP at unit, endoscopist, and pathologist level.

The data extraction for this study was limited to those individuals who had attended for post-polypectomy surveillance. Analyses using the outcome of adenoma (and specifically advanced adenoma) rate at surveillance required that at least one surveillance had been attended in order to assess for the presence or absence of AA. Results of analyses using CRC as outcome could be compared to a number of potential comparator groups: those with low risk findings at FOBT positive screening (and so not recalled for any surveillance), those recalled for surveillance who did not attend, or those eligible for FOBT screening who did not participate. However, at the time of data extraction and analysis, these data were not available from PHE as linking of data from NCRAS was not complete.

An important complementary analysis is that reported by Atkin from outwith the BCSP[66]. This study included individuals with intermediate risk findings at

baseline of whom 58% had attended at least one surveillance and 42% had not attended any surveillance. It was found that, overall, attending at least one surveillance was associated with a reduction in CRC risk over a mean 7.9 years follow-up (adjusted hazard ratio 0.57 for one visit). Without surveillance, colorectal cancer incidence in patients with a suboptimal quality colonoscopy, proximal polyps, high-grade dysplasia or adenoma ≥20 mm at baseline was significantly higher than in the general population (SIR 1.30, 95% CI 1.06-1.57). However, in the absence of these features, CRC incidence was lower than that of the general population (SIR 0.51, 95% CI 0.29-0.84). These findings illustrate that the benefit of surveillance may be limited to a higher risk subgroup of those currently recalled for post-polypectomy surveillance.

Modality of screening and surveillance

Screening for colorectal cancer may be performed by a number of investigation modalities, alone or in combination. Colonoscopy is considered the gold standard investigation. However, colonoscopy is an expensive, time consuming, and uncomfortable investigation with a small risk of serious complications. Primary screening colonoscopy is advised in relatively few countries; notably the USA and Poland. Alternative tests include flexible sigmoidoscopy, CT colonography, and faecal blood tests: gFOBT (guaic faecal occult blood test) or FIT (faecal immunochemical test).

The faecal blood tests are used to triage which individuals require further investigation[37], usually by colonoscopy. CT colonography allows radiological visualisation of the colorectum without the need for colonoscopy. This is often seen as more acceptable to patients. However, the examination does require bowel preparation and carries a risk of bowel perforation due to the need for carbon dioxide insufflation of the colon. CT colonography is a relatively expensive test to be used as a means of triage for colonoscopy. Therefore, CT colonography is not advised as a standard screening investigation, but generally used as an alternative examination for individuals with a specific reason to avoid colonoscopy: incomplete colonoscopy, difficult or painful colonoscopy previously, necessity for continued anticoagulation, or relative contraindications to full bowel preparation for optical colonoscopy.

Flexible sigmoidoscopy has some advantages over colonoscopy as a screening test: simplified bowel prep with enema only, shorter procedure time and associated lower costs. Like colonoscopy, the procedure is invasive and carries a small risk of serious complications. In addition, the proximal colon is not visualised and so it is logical that protection against CRC of the proximal (right) colon would be inferior to colonoscopy. The rationale for the use of flexible sigmoidoscopy in screening is that two thirds of CRCs are located in the rectum or sigmoid colon. The UK Flexible Sigmoidoscopy Screening Trial (UKFSST) recruited individuals aged 55 to 64 years from 1994 until 1999 with the aim of determining the effect of a once only sigmoidoscopy on CRC incidence and mortality. Results of seventeen years' follow-up have recently been reported[113], showing enduring benefit with a reduction of 26% CRC incidence and 30% CRC mortality. This supports the addition of once only flexible sigmoidoscopy at age 55 years through the "Bowelscope" screening programme in the UK.

Many countries, including the UK, use a combination of these tests[114].

Colorectal adenomas: The New "Normal"?

Adenoma detection rate in primary screening colonoscopy may be as high as 70%[115] if using a very long withdrawal time and has been reported as 43% in FIT-positive screening subjects in normal practice at a threshold of 100 ng/mL (20µg/g)[116]. Given that finding at least one adenoma at colonoscopy in a screening age group may be as likely as finding none, can the presence of colorectal adenomas be said to convey increased risk of CRC? The general population risk to which this risk is compared refers to a population where nearly half of individuals possess at least one adenoma.

The pathology yield at colonoscopy raises difficult questions on which diagnoses are important and what likelihood of a significant diagnosis warrants investigation. In the UK overall, colonoscopy detects CRC in 3% of procedures. Diagnostic yield in "two-week" suspected colorectal cancer referrals has been reported to be 9-10%[117,118]. In primary screening colonoscopy, CRC incidence is 0.5–0.6%[119,120]. In the gFOBT positive screened cohort of the BCSP, the incidence of CRC at screening in the prevalent round is 9.4%. In a FIT positive screening cohort at a level of 100 ng/mL (20µg/g), the CRC incidence at colonoscopy is up to 8.6%[116].

Interpretation of these figures raises a fundamental question: what yield of pathology, or likelihood of finding a cancer or an advanced adenoma, or any

adenoma is sufficient reason to perform a colonoscopy? There can be no absolute answer to this question and in reality the answer must be personalised to the individual and the healthcare setting. However, in the era of population screening for CRC, there must also be a threshold at which a screening programme deems colonoscopy to be warranted in an asymptomatic individual. As shown in the results presented in this thesis, the English BCSP currently performs screening colonoscopy when the chance of detecting CRC is 9.4% (FOBt+), but also performs post-polypectomy surveillance when the chance of detecting CRC is less than 0.5%. If the BCSP deems 0.5% CRC risk as the correct threshold to perform colonoscopy, then the logical conclusion must be that primary colonoscopy, and not FOBt or FIT, should be the modality of screening. However, there is an alternative rationale for post-polypectomy surveillance colonoscopy when the yield of CRC is very low: the aim of surveillance is different to that of screening.

Screening aims to detect cancer at an earlier, asymptomatic stage. Surveillance allows detection and resection of pre-cancerous lesions with the aim of preventing CRC. Therefore, the best measure of success of surveillance in this aim would be to demonstrate a reduction in CRC incidence among a group taking part in post-polypectomy surveillance compared to a matched group with no surveillance after resection of adenomas. As discussed in the introduction to this thesis, such a randomised trial is unlikely to be performed. In its place, advanced adenoma incidence may act as a surrogate marker to

guide decisions on which groups are most likely to benefit from surveillance. A recent study of post-polypectomy surveillance in the intermediate risk group in the UK showed that there was benefit to some individuals, but that this was dependent upon the presence of additional factors of an adenoma ≥20mm, proximal polyp(s), a suboptimal colonoscopy examination, or high grade dysplasia[66].

PCCRC

A post-colonoscopy colorectal cancer (PCCRC) has been defined as a CRC diagnosed within a three or five year period following a colonoscopy at which no CRC was diagnosed. A recent study of the BCSP in England found a PCCRC rate of 2.09%[121]. However, this figure underestimates the true PCCRC rate as data for interval cancers that presented symptomatically external to the BCSP were not available for analysis. Published literature from England during a similar time period of 2001 to 2007 found a PCCRC rate of 8.6%[122].

In this thesis, data have been presented showing the true rate of CRC diagnosis, including interval CRCs, for individuals who attended for post-polypectomy surveillance in the BCSP. The mean and median follow-up time of 4.1 years from baseline FOBt+ colonoscopy is in line with the definition of a PCCRC. By definition, these individuals have attended at least once for a repeat examination of the colon. As such, it may be have been expected that the rate of CRC in this cohort would be higher than in a non-surveillance

cohort as asymptomatic early cancers can be diagnosed. The analysis presented here in shows the proportion of the cohort diagnosed with a CRC was very low and much lower than the figures reported in the BCSP as a whole or in the non-screening NHS symptomatic service.

Defining increased risk

Multiplicity

The detection and resection of multiple adenomas has been identified as a risk factor for future colorectal neoplasia compared to detection and resection of a single adenoma. However, it is notable that detection of small polyps by CT colonography is unreliable and that lesions of less than 5mm in size are not reported for this reason. Therefore, a CT colonography performed for either screening or surveillance in the BCSP may detect several polyps, all of less than 5mm diameter, and be reported as "normal". As a result, no polypectomy would be performed, and any further surveillance plan would be based on no polyps being present at the BCSP episode in question. If, however, a colonoscopy had been performed instead of a CT colonography for the same BCSP episode and the same multiple small polyps had been detected, then these lesions would have been reported and resected. If at least five small lesions were concluded to be adenomatous, then the episode outcome would be "high risk" and the individual recalled for further surveillance twelve months subsequently. This inconsistent scenario cannot be further analysed

from the data available as the CT colonography data entered into BCSS would be based on the report stating "no polyp".

"Advanced adenoma"

As noted in the above systematic review, multiple definitions have been used in the literature for the entity of "advanced adenoma". While the definitions are similar, this variation does result in heterogeneity of evidence for the factors conferring increased risk of colorectal neoplasia and particularly "advanced" neoplasia.

The common definition of an advanced adenoma is the presence of any one of the following features: diameter of at least 10mm, high grade dysplasia, or villous architecture ≥25%. This was the definition used in this thesis. Taking each of these features in turn, the accuracy of diagnosis must be considered. Firstly, diameter can be measured either by the endoscopist or the pathologist. Where endoscopic size is used, this is an estimated size and is known to vary significantly from the reported histology size for the same lesion. Histology size may be affected by shrinkage due to the fixing solution and can be reported as either maximal diameter of the entire lesion or of the adenomatous component (as advocated within the BCSP). Additionally, both endoscopy and histology size are subject to terminal digit preference (as borne out by the BCSS data analysed for this thesis). It has been suggested that terminal digit preference may have a greater effect close to the threshold of 10mm due to the

knowledge that reporting 10mm rather than 8mm or 9mm will impact upon surveillance recommendation.

Grading of dysplasia is prone to inter-observer variability due to the multiple histologic features used to define high-grade dysplasia.

Likewise, villous architecture can be defined as equal to, or greater than, 25% villous architecture. This definition allows for variation in reporting due to varying reporting of villous and tubular architecture and variation in sizing of the lesion as described above. Therefore achieving the 25% threshold may be affected by either the numerator (villous component) or denominator (total lesion size).

Defining surveillance

Surveillance is re-examination of the colorectum at a time interval following complete resection of all detected adenomas.

In the context of post-polypectomy colonoscopy, there are multiple scenarios whereby an individual may attend for further colonoscopy or sigmoidoscopy after detection of adenoma(s). In this thesis, as in the published literature, the term "surveillance" implies that a complete examination of the colorectum has been performed and that all detected lesions have been resected completely.

There are other situations in which repeat endoscopic procedures are performed and therefore at which further adenomas may be detected. A single colonoscopy may detect lesions which cannot be resected at that time. For example, if the individual is anticoagulated due to concurrent medication, the required endoscopist, endoscopy team, or equipment is not available at that time, or endoscopist or patient fatigue causes the procedure to be discontinued before all lesions have been resected. Such scenarios require further colonoscopy, but should be considered part of the same "episode" of care (as is the case in BCSS). A further procedure may also be planned (generally at a three to six month interval) after resection of a large lesion, in order to assess for any residual adenomatous tissue or early recurrence. Again, this should be considered part of the same episode of care and is not surveillance.

It is accepted among endoscopists that the knowledge of a further procedure in the near future may influence endoscopist behaviour such that reporting can be affected. For example, a prolonged procedure to remove a large adenoma in the proximal colon may cause endoscopist and patient fatigue. After resection of this large lesion, many factors contribute to reduced likelihood of detection of further lesions in the more distal colon. Firstly, retrieval of the resected lesion usually requires use of a Roth net and a resultant reduced field of view on withdrawal of the colonoscope. Secondly, the endoscopist's fatigue and distraction of a large lesion already detected reduces the chance of further lesion detection. Additionally, the knowledge that a further colonoscopy will

be performed (in three to six months' time) means the endoscopist may not feel it necessary to detect other smaller lesions at this procedure.

Unpublished literature (personal communication, W. Atkin) from analysis of post-polypectomy surveillance in intermediate risk individuals in the UK symptomatic service suggests that findings at first surveillance at a three year interval are similar to findings at earlier follow-up colonoscopy. It is possible that a second ("tandem") colonoscopy performed on the same day is likely to detect the same pathology as one performed at an interval of three years. This supports the concept of first surveillance being considered a "clearing" colonoscopy where lesions that were present but not detected previously can be detected and resected. This concept is widely accepted in the setting of high risk findings and first surveillance at a one year interval.

Of note, tandem colonoscopy is known to detect more lesions, but slower withdrawal time over ten minutes has not been shown to significantly increase adenoma detection[123].

Polyposis syndromes

It must be noted that a small number of subjects possessed a sufficiently high number of adenomas that an underlying polyposis syndrome must be considered. Adenomatous polyposis syndromes include FAP (familial adenomatous polyposis) and MAP (MUTYH-associated polyposis). More

recently, serrated polyposis syndrome (SPS) has been recognised. As discussed elsewhere, the definition of a serrated polyp has been updated during the time period covered in the data analysis for this thesis. Therefore, while a diagnosis of SPS can be made based on the number, location, and size of serrated polyps, retrospective identification of cases of serrated polyposis can be problematic.

Current clinical guidelines suggest consideration of germline testing in individuals found to have at least ten adenomas: less than 3% of the total cohort analysed in this study would fall into this category. While many demographic and medical history details are documented in BCSS, and were analysed in this study, it is a limitation of the data that other factors known to be associated with CRC risk are not included: a personal history of polyps or CRC, family history of CRC, or a diagnosis of inflammatory bowel disease. These factors are likely to modify the risk of those individuals affected but have not been controlled for in analyses. In practice, specific clinical guidelines should be followed for these patient groups and recommendations on post-polypectomy surveillance be applied to the general population not belonging to an identified higher risk group.

Retrospective data

Given the slow progression to cancer via the adenoma-carcinoma sequence, a long follow-up duration is required to assess effects on cancer incidence. This

poses a significant barrier to prospective trials of adenoma surveillance. Furthermore, the clinical practice of offering surveillance to individuals diagnosed with adenomas falling into the current intermediate and high risk groups, is well established over more than 15 years. As such, there would currently be concerns over the ethics of a prospective trial of surveillance compared to no surveillance in these groups.

Retrospective data present the opportunity for study of these groups over a time period of more than ten years. However, retrospective data have inherent limitations. Data quality is often poor compared to that collected during a prospective research trial. In this setting, data are commonly sourced from hospital or regional databases. As such, there is much heterogeneity in data format, completeness, and reliability. Paramount to adenoma data, is the linkage of endoscopy and pathology reports. This linkage must usually be performed by the researcher in order to prepare the data for analysis as pathology and endoscopy databases are separate IT systems.

In endoscopy research, there is an additional limitation in retrospective data being used to achieve a longer follow-up duration. Quality in endoscopy is ever increasing. This is due to numerous factors: advances in technology and equipment, improved training of endoscopists, and an increased emphasis on and scrutiny of performance indicators. The UK leads the world in endoscopy training and quality. Key milestones in the development of today's high

quality service were the BSG national colonoscopy audit in 2004, implementation of the current Joint Advisory Group (JAG) accreditation process in 2005, and establishment of the English BCSP in 2006.

The data analysed for this thesis represents the first opportunity to assess a ten year period since the development of high quality colonoscopy in the UK. BCSP data specifically represents the clinical picture in a quality assured service and shows what can be achieved in this setting.

Generalisability

It could be argued that the high quality colonoscopy performed within the BCSP is not representative of general endoscopy practice in the NHS. It is true that quality standards in the BCSP are more stringent than in the general symptomatic service. However, quality standards in endoscopy in the UK are continually improving. The 2004 BSG national colonoscopy audit revealed an unadjusted caecal intubation rate (CIR) of just 76.9%. A repeat audit of over 20,000 colonoscopies in 2011 showed this figure had improved to 92.3% and that the polyp detection rate (PDR) was 32.1%. The findings of this thesis serve as a further driver to continue to improve colonoscopy quality standards in all settings. These results show what can and is being achieved in a high quality colonoscopy service.

Personal reflection

I qualified as a doctor in 2006 and specialised in gastroenterology in 2012. I was attracted to the specialty by a number of factors including the diverse disease processes falling under the care of a gastroenterologist: acute and chronic conditions which may be inflammatory, infective, or functional. I was drawn to the opportunity for a diverse working life: outpatient and inpatient clinical work, the practical skills of performing endoscopic procedures, and the allied academic role in teaching and research.

Over the years in clinical medicine, my viewpoint on many aspects of clinical practice has changed. Medicine is changing rapidly at a time of unprecedented ageing of the population, particularly in developed nations. As a medical student, I was taught that the specialty of geriatrics was concerned with caring for "elderly" patients over the age of 65. Now, less than fifteen years later, such an age boundary seems perverse: the majority of hospital inpatients are over 75 and the average age is now over 80[124]. A census performed at one hospital indicated that the average age of medical patients was 82 years and that 10 per cent of patients were over 92[125].

Current BSG guidelines suggest that adenoma surveillance be discontinued at age 75. This approach is followed by the English BCSP and in many other developed countries. The rationale for this decision is sound: the risk of complications from colonoscopy and polypectomy increases with the patient's

age, while the progression of an adenoma to cancer occurs over a sufficiently prolonged time period that the individual must have a long life expectancy to be likely to benefit from polypectomy. At least one English NHS Trust has published a policy of not routinely performing polypectomy in any patient over the age of 85 and discouraging those aged over 80 from continuing surveillance[126].

Conversely, the risk of an unresected adenoma progressing to cancer is increased with advancing patient age.

It is difficult to be prescriptive about a defined age threshold at which to discontinue surveillance. A key factor influencing this decision must be the individual patient's life expectancy. In the era of individualised medicine and shared decision making, it is incumbent upon all colonoscopists and clinicians to discuss these issues with their patient.

The process of completing this PhD has included periods of frustration with slow progress and at times, doubt that the project could be completed. In particular, gaining access to the data from BCSS was problematic and achieved only in January 2017, with additional data on cancers and deaths received late in 2017.

Access to data

Bowel Cancer Screening data falls under the auspices of Public Health England. Access to the data for research purposes is controlled by the Office for Data Release. During the application process for my data request, the issue of data protection was in the spotlight. A new European Parliament directive on "the protection of natural persons with regard to the processing of personal data and on the free movement of such data", was adopted in May 2016.

Under the NHS Constitution, patients have the right to object to their identifiable data being shared with other organisations for purposes other than their direct clinical care. This objection includes purposes such as research. These "type 2" objections must be registered with the patient's GP. Since April 2016, data pertaining to "type 2 objectors" has been excluded from data shared for research purposes. In December 2016, 2.3% of patients in England were registered as a "type 2 objector". However, there are reports of GP practices objecting en bloc on behalf of all their registered patients. Indeed, there are multiple GP practices where 100% of their registered patients have a "type 2" objection.

Access to health data for research purposes is an evolving field. The data analysed for this thesis were provided to me in "pseudo-anonymised" form with each data subject being identified only by a unique study identification number. No geographical data was provided and so some analyses such as

comparing screening hubs, centres, or endoscopists, or assessing the effect of deprivation index (using residential postcode) could not be performed.

In order to convert the data provided by PHE into a format which could be analysed, multiple tables of data had to be combined into a "flat" file. This process was very time consuming and represented far greater proportion of the workload than the subsequent analysis. During processing, very large Stata datasets were used: due to there being up to 8,000 variables and over 80,000 observations per file, Stata files of over eight gigabytes of data were created.

Project evolution

At the inception of this project in early 2015, there were two related aspects of adenoma surveillance which I considered for further study. Firstly, as noted by the authors of current clinical guidelines in the UK and abroad, the evidence base on which to recommend post-polypectomy surveillance is sparse and recognised as an area requiring further research. Secondly, the decision making process by which individuals elect to engage with a surveillance programme is an essential component in efforts to reduce colorectal cancer mortality. If the recommendations laid out in clinical guidelines are not widely followed, the expected effect on cancer incidence and mortality cannot be realised.

Clinical guidelines

Current clinical practice in the UK is based on two sets of guidelines published by the British Society of Gastroenterology (BSG) and the Association of Coloproctology for Great Britain and Ireland (ACPGBI) in 2010, and by the National Institute for Health and Clinical Excellence (NICE) in 2011. These documents set out recommendations that individuals found to have adenomatous polyps at the time of colonoscopy be classified by colorectal cancer risk and be offered surveillance colonoscopy determined by this risk category.

Clinical guidelines are not intended as rules to be applied in all clinical situations. By their very nature, they offer recommendations which are intended to be seen as a guide to the clinician. There are numerous reasons that the recommendation of a clinical guideline may not be the followed in a clinical scenario. The patient's wishes are a key factor and often not considered in guideline documents. My own experience in clinical practice is of highly variable adherence to guidelines. In the area of polyp surveillance, practice is variable from one hospital to the next, in my own experience of working in NHS endoscopy units around the north east of England.

Shared decision making (SDM)

In 2012, the Kings Fund published a report on the use of Shared Decision Making (SDM) in the NHS. The report observed that while doctors believe they know what their patients want, there is evidence to suggest this is not the case. The term "preference diagnosis" refers to the healthcare professional's understanding of the patient's wishes. It was suggested that in current practice, doctors feel that they know what a patient would choose after spending time with the patient during, for example, a clinic consultation. It is the assertion of the report authors, and backed up by evidence, that doctors frequently do not determine the patient's wishes accurately.

Three major advantages were suggested for more widespread use of SDM:

1. Ethical – The autonomy of the individual patient can only be respected after the patient has been given the opportunity to make an informed decision.
2. Policy – Long term service provision relies on planning, which must be informed by patient preference in order to develop services meeting the population's needs.
3. Financial – It has been shown repeatedly that consumption of health resources falls when patients are given a choice in their investigation and treatment using SDM.

The Kings Fund report estimated that, across the NHS, using SDM to determine all investigations and treatment, could save a total of £30 billion, equivalent to 16% of the total 2022 NHS budget.

Shared Decision Making is particularly applicable to decisions around screening or surveillance due to its preventative intent. The population being considered are not patients, but a section of the population at large. In making the decision to participate in screening and subsequently surveillance, the individual must weigh the risks of participation, including the risks of colonoscopy, in a different setting to that of patients with symptoms. The planned, elective nature of screening and surveillance also allow for the required time to engage in SDM.

I considered a number of qualitative studies to investigate the use of SDM in post-polypectomy surveillance. These studies were based on the different groups of individuals involved in the decision making process. In order to determine what process has been followed in practice, I planned to interview patients already enrolled in post-polypectomy surveillance about their recollection of discussions at the point of being diagnosed with colorectal adenoma(s) and embarking upon surveillance.

Secondly, opportunistically interviewing individuals newly diagnosed with colorectal adenoma(s) regarding their understanding of the diagnosis,

knowledge of CRC risk and surveillance plan, and their wishes for involvement in the decision process around surveillance.

Finally, I intended to interview clinicians involved in decisions around post-polypectomy surveillance. These clinicians would primarily be consultant gastroenterologists and surgeons who perform colonoscopy. The aim of this study was to explore current beliefs around the use of surveillance and adherence to guidelines as well as investigating how receptive clinicians would be to a change in surveillance practice based on new evidence.

During the planning stage of these studies, I presented the proposal in a number of fora. My application to present my proposal to the National Cancer Research Institute (NCRI) Screening, Prevention, and Early Diagnosis (SPED) group was successful and I addressed the panel at a research workshop in November 2015. In addition, I discussed the planned studies at the Northern Region Endoscopy Group (NREG) meeting. Feedback from experts and researchers in the field was that the BCSS data analysis plan was important research to perform, but that the intended SDM qualitative studies could be largely negated by the BCSS analysis. As the hypotheses of the BCSS data analysis centred around a reduction in post-polypectomy surveillance, it was considered that the results from this analysis should be available and considered prior to any SDM study being performed. Therefore, my focus

concentrated on the quantitative work of BCSS data analysis, preceded by a systematic review of the literature.

Donabedian model

Avedis Donabedian developed a conceptual model[127] which has, for the past fifty years, been recognised internationally as a framework for evaluating the quality of healthcare. The model can be summarised in the following form:

Structure + process = outcomes

The three variables identified in this model can be measured as an indicator of quality. Each parameter has advantages and disadvantages as a measurable indicator. The ultimate measure of quality in healthcare is that of outcomes. However, there are barriers to achieving such measurement. There is variation in the expected outcome dependent upon: patient factors such as co-morbidity, severity of illness, socio-economic group; and external factors such as the quality and availability of local services. Another measurement challenge is the time lag between the care intervention and the outcome of interest.

A potential criticism of this study is the use of advanced adenoma detection as an endpoint in many analyses. The aim of the Bowel Cancer Screening Programme is the early detection and prevention of colorectal cancer through polypectomy. Therefore, the most pertinent outcome is that of colorectal cancer. However, to focus on cancer alone would severely limit the possible analyses of the data for the reasons identified by Donabedian.

Focus on the process of advanced adenoma detection and resection acts as a marker of potential cancer development. Colorectal cancer is unusual in possessing a detectable precursor lesion. This presents the opportunity for cancer prevention through polypectomy, but also for the study of the precursor lesion as an intermediate outcome on the pathway to cancer development.

Carcinogenesis and the serrated pathway

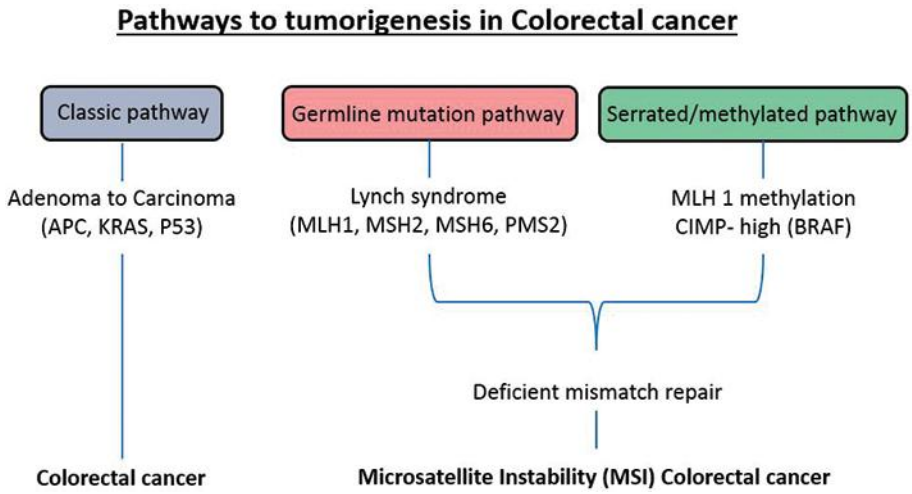

Figure 8 - CRC pathways

Current understanding of colorectal cancer development is that three genetic pathways exist. The majority of cancers develop through the classical pathway from conventional adenomas. It was this pathway on which this thesis concentrated. However, it is recognised that colonoscopy has a lower protective effect against proximal (right) colon cancers. It is postulated that the serrated pathway of carcinogenesis is the reason for this differential protective effect in the right and left colon.

Serrated lesions of the colorectum were previously described as "hyperplastic" and believed to have no malignant potential. Therefore, these lesions were often not reported or resected at colonoscopy. The classification of serrated lesions was updated in 2010 by the WHO (World Health Organisation) and

includes four entities as described in Table 64 - Taxonomy of serrated lesions. It is sessile serrated lesions (SSLs) of the proximal colon that have become a focus of attention in recent years. These lesions may become dysplastic and can then be subcategorised as an SSLd (sessile serrated lesion with dysplasia).

	Morphology	**Size**	**Prevalence**	**Colonic location**	**Malignant potential**
Hyperplastic (HP)	Flat or sessile	Usually ≤5mm	Very common	Left colon	N
Sessile serrated lesion/polyp (SSL/SSP)	Flat or sessile	Usually >5mm	Common	Right colon	Y
Traditional serrated adenoma (TSA)	Sessile or pedunculated	Usually >5mm	Rare	Left colon	Y

Table 64 - Taxonomy of serrated lesions

The serrated pathway is believed to progress at a differential rate to the conventional adenoma-carcinoma pathway[128,129]. This potential for rapid progression to invasive cancer leaves a short window of opportunity to detect and resect serrated lesions before malignancy develops.

The future of screening and surveillance

This thesis has made reference to colonoscopy as the gold standard of colorectal investigations. However, the diagnostic utility of colonoscopy must be balanced against its inherent disadvantages of being costly, time consuming, uncomfortable, and carrying risk of complications. Alternative investigation strategies have been explored as discussed in the section "Modality of screening and surveillance" above. Current research is developing additional modalities which may impact on future surveillance practice.

Colon capsule- Capsule endoscopy has become an established modality of investigation of the small bowel. The same technology may be used to perform a colon capsule examination. This modality is attractive in avoiding the potential discomfort of conventional optical colonoscopy. However, bowel preparation is still necessary and there are a number of disadvantages: polypectomy cannot be performed, biopsies cannot be taken, reading of the images can be time consuming with resultant resource-use implications. In terms of polyp detection, colon capsule has the advantage of obtaining both antegrade and retrograde views. Therefore, polyps that could have been hidden behind folds during conventional colonoscopy may be visualised. However, it is not possible to insufflate the colon or to suction fluid or debris from the lumen. As a screening modality, colon capsule has a major disadvantage in requiring a second procedure with colonoscopy for

polypectomy in the large proportion of individuals in whom polyps are present at screening.

Urine- A novel urine-based metabolomic diagnostic test for the detection of adenomatous polyps, PolypDx™ (Metabolomic Technologies Inc. (MTI), Edmonton, AB, Canada). One-dimensional nuclear magnetic resonance spectra of urine metabolites were analyzed to determine the concentrations of three key metabolites. Sensitivity and specificity for the presence of colorectal polyps were 82.7% and 51.2%, respectively[130].

Robotic colonoscopy- An endoscope which is propelled around the colon by means of magnets is under development. The potential advantage of such technology may be in improved patient comfort through use of a slimmer and more flexible scope with no need for transmission of pushing forces to advance the tip of the instrument. It is also suggest that such an endoscope could be more manoeuvrable in retroflexing at any colonic location and so aid lesion detection. Animal trials are in progress[131].

Future research

Synthesising evidence from the scientific literature on colonoscopy quality, post-polypectomy surveillance, and the new evidence presented in this thesis, there are salient points on which further clinical research can be advised.

The "miss rate" for polyps at colonoscopy is known to vary with size of polyp and is evidenced by tandem colonoscopy studies. Evidence presented in this thesis and elsewhere shows the likelihood of further adenomas being detected at repeat colonoscopy is influenced by the significance of the neoplasia detected at baseline. It could be argued that this is due to either a propensity to neoplasia (new lesions) or missed pathology. The miss rate of colonoscopy is one reason for the general acceptance that the majority, if not all, neoplasia detected at a one, or even three, year interval was present at baseline: "missed lesions".

Therefore, surveillance is not "surveillance" by its pure definition: it is based on the understanding that the colon was *not* completely clear of neoplasia at baseline despite the best efforts of the colonoscopist. Repeating the colonoscopy at a one or three year interval may be more correctly defined as a "clearing" exercise.

If the true purpose of repeating a colonoscopy after one or three years is to find the neoplasia missed previously, the key question is what can be done at baseline to improve detection and potentially negate the benefit of repeating the colonoscopy at a later date.

The BCSP recommends a minimum "negative withdrawal time" for colonoscopy: the time spent inspecting the mucosa as the colonoscope is

withdrawn from the caecum to the rectum (excluding any time spent performing polypectomy). This recommendation is based on evidence that withdrawal time is correlated with adenoma detection. There is an increase in adenoma detection associated with increasing withdrawal times up to ten minutes, with the greatest increase seen up to a withdrawal time of at least six minutes. On this basis, the BCSP advises a minimum withdrawal time of six minutes and a target of ten minutes. Therefore the optimum withdrawal time is used in colonoscopies performed in the BCSP and evidence suggests there would be no significant increase in detection by further prolonging withdrawal time.

If the neoplasia detected at repeat colonoscopy is present at baseline, it could be argued that the time interval to repeat colonoscopy does not matter. The most efficient time to perform this repeat examination would in fact be immediately: at the time the individual has taken bowel preparation, travelled to the endoscopy unit, and been given sedative medication if required.

The miss rates quoted based on tandem colonoscopy studies show that a tandem colonoscopy is more effective than any adjuncts in increasing adenoma detection. In tandem colonoscopy studies, one endoscopist completes a colonoscopy and then a second endoscopist performs another colonoscopy. The use of two endoscopists is clearly a resource-intensive practice with significant cost implications. Could the second colonoscopy be

performed by the same endoscopist? In a recent study of polyp detection in the proximal colon, reintubation and extubation of the colonic segment was found to significantly increase polyp detection in that segment, suggesting re-inspection by the same endoscopist may have a similar effect to repeat colonoscopy by a second endoscopist. Such a strategy would be more feasible in clinical practice from a logistical and cost perspective.

The potential approaches to research the efficacy if this approach could be retrospective: including subjects of previous tandem colonoscopy trials, or prospective in a randomised trial. As with all surveillance research, a prospective trial would by definition have a significant time interval before reporting results. Such a randomised trial could be designed with three arms at baseline colonoscopy:

1. standard single colonoscopy with six to ten minute withdrawal time
2. tandem colonoscopy with extubation to the rectum followed by reintubation to the caecum and a second full withdrawal phase
3. segmental reintubation colonoscopy: for each colonic segment, the colonoscope is withdrawn through that segment before that segment is reintubated and a second withdrawal performed through that segment.

A large multinational European study is currently recruiting subjects with the aim of addressing the question of optimum post-polypectomy surveillance. The EPoS (European Polyp Surveillance) studies[132] comprise two randomised

trials, and one observational study. EPoS study I will randomise 13,766 patients with low-risk adenomas (1–2 tubular adenomas size <10mm with low-grade dysplasia) to surveillance after 5 and 10 years, or 10 years only. EPoS study II will randomise 13,704 patients with high-risk adenomas (3–10 adenomas; or adenoma ≥10mm in diameter, or adenoma with high-grade dysplasia or >25% villous features to surveillance after 3, 5 and 10 years, or 5 and 10 years only. EPoS study III will offer surveillance after 5 and 10 years to individuals with serrated polyps ≥10mm in diameter at any colorectal location, or serrated polyps ≥5mm in diameter proximal to the splenic flexure, and is an observational study.

CRC incidence after 10 years will be the primary endpoint. It is anticipated that the EPoS studies will, for the first time, provide prospective randomised trial evidence for different post-polypectomy surveillance strategies. However, due to the large number of subjects to be recruited and a long surveillance period, results will not be available for many years.

In the UK, the BCSP represents an excellent opportunity for prospective research of post-polypectomy surveillance. As a centrally administered national programme with excellent coverage of the population, eligible individuals could be identified and recruited relatively easily. The hub and spoke organisation of screening centres could facilitate a cluster randomised

trial of surveillance strategies. For example, each screening hub could randomise its screening centres to a surveillance strategy.

Surveillance strategies used in such trials should be designed to answer questions of optimal surveillance interval as well as the best factors to use in risk stratification. To this end, screening hubs could randomise centres to offer the high risk surveillance group to current surveillance (at years 1 and 4) or to first surveillance at an interval of three years. The intermediate risk group could be randomised to current first surveillance at three years or to no colonoscopic surveillance (and therefore return to stool test screening). This approach would allow analysis of key endpoints (CRC incidence, rate of AA at first surveillance) in delayed surveillance. In addition, if centres were randomised to strategies separately for the high and intermediate risk groups, then some centres would perform all surveillance at an interval of three years. Analysis of data from these centres could be used to address the question of the best method of risk stratification. The data presented in this thesis shows a particularly low risk of metachronous neoplasia in those with a single adenoma at baseline. However, other factors not available for analysis in the current BCSS dataset could also be explored. For example, a personal history of inflammatory bowel disease, a family history of CRC, and the regular use of aspirin.

Such analysis may allow a new risk stratification method to be implemented and so greatly reduce the number of individuals recalled for surveillance. First surveillance outcomes in this study would be available for analysis three years after recruitment, and so have the potential to alter clinical practice sooner than results from the EPoS trials.

Conclusion

The analyses presented in this thesis have shown a number of important outcomes of post-polypectomy surveillance in the English BCSP:

1. CRC rates among the surveillance cohort in the BCSP are low.
2. Individuals qualifying as "intermediate risk" by resection of a single adenoma of at least ten millimetres diameter have a particularly low subsequent risk of advanced colorectal neoplasia.
3. The number of adenomas at baseline was seen to be more strongly predictive of surveillance findings than the size of the largest adenoma at baseline.

Of individuals with high risk findings at baseline, 12.3% of those attending first surveillance were found to have at least one advanced adenoma (AA), 48.0% non-advanced adenoma, 39.1% no adenoma, and 0.5% CRC.

In the case of individuals with intermediate risk findings at baseline, of those attending first surveillance, 8.0% were found to have AA, 35.3% non-advanced adenoma, 56.1% no adenoma, and 0.4% CRC. Among those categorised as intermediate risk based on the finding of a single adenoma (≥10mm) at baseline, 6.3% of those attending first surveillance were found to have AA and 0.3% CRC.

The most significant factor increasing the risk of AA at first surveillance was a higher total number of adenomas at baseline colonoscopy.

In addition to the current classification using size and number of adenomas, there are additional adenoma factors which modify risk in those individuals attending for post-polypectomy surveillance, such as villous architecture, as well as person factors such as age and gender.

These findings will influence future clinical practice in the UK through revision of clinical guidelines. Revision of the UK (2010) guideline is in progress at the time of writing. The Guideline Development Group includes representatives from the British Society of Gastroenterology (BSG), Public Health England on behalf of the BCSP, and The Association of Coloproctology of Great Britain and Ireland (ACPGBI). The guideline development process is compliant with National Institute for Health and Care Excellent (NICE) procedures. As such, the clinical guideline will be endorsed by the BSG, BCSP, ACPGBI, and NICE. The results of the above analyses have been submitted and internally peer reviewed by the Guideline Development Group. These findings are being considered alongside the published literature and results of other recent studies when determining clinical recommendations.

The findings of this large study of robust data provide evidence to support a significant reduction in post-polypectomy surveillance. While these findings

are particularly relevant to the BCSP as an organised and quality assured programme, current practices and quality monitoring outside the BCSP are now much more robust. As such, these analyses can be considered broadly generalisable on the basis of high quality baseline colonoscopy.

The findings presented in this thesis represent a strong evidence base on which to discontinue the practice of post-polypectomy surveillance for individuals with a single adenoma at baseline. Moreover, given a similar AA rate at first surveillance in the intermediate risk group compared to primary screening colonoscopy in other Western countries[22,27,133-135], these findings support the discontinuation of surveillance for the entire intermediate risk group.

Such a significant shift in practice would positively impact upon endoscopy capacity at a time of increasing indications for colonoscopy (including FIT testing), as well as reducing the burden of repeat colonoscopy for patients.

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APPENDIX 1

Data analysis methods

1.1. Data received

1. Subject Table

a. Subject_ID (unique study ID created by the PHE Screening Team prior to transfer)

b. Gender (M / F)

2. Episode Table

a. Subject_ID

b. Episode_ID

c. Age_Epi_Start (in years)

d. Episode_Status (Closed / Open / Pending)

e. Episode_Type (Screening / Surveillance / FS Screening)

f. Prevalent_Incident

g. Episode_Seq_No (Number of episode in sequence in which the individual subject has participated. Note this sequence also includes episodes of a submitted gFOBt which does not result in a diagnostic test.)

h. Episode_Result (Cancer / High-Risk / Int-Risk / Low-Risk / Abnor-No-Histology / Abnormal / Normal / Blank / No-Result. Note that "Abnormal" results indicate no cancer and no adenoma.)

3. SSP Fitness Assessment Table (Episode-level data, therefore multiple entries may exist for an individual subject)

a. Subject_ID

b. Episode_ID

c. Height_(m)

d. Weight_(m)

e. Alcohol (Yes / blank)

f. Alcohol_Units/Week

g. Smoker (Yes / No / Ex-Smoker / Not Known)

h. ASA grade (I – Fit / II – Relevant disease / III – Restrictive disease / IV – Life threatening disease / V – Moribund / Not Applicable / Not Known)

4. Diagnostic Test Table

a. Subject_ID

b. Episode_ID

c. Diag_Test_ID

d. Test_Date

e. Test_Sequence (within the episode)

f. Test_Type (Colonoscopy / Limited Colonoscopy / Flexible Sigmoidoscopy / FS Screening Test / Virtual CT Colonoscopy / Abdominal CT Scan / Barium Enema / Scan (x-ray))

g. Outcome (Cancer, Refer MDT / High-risk Polyps / Intermediate-risk Polyps / Low-risk Polyps / Abnormal, not Polyps / Normal / Refer to Surgery / Refer Colonoscopy / Complete – Refer Another / Incomplete – Refer Another / Cancel Diagnostic Test / DNA Diagnostic Test / Consent Refused, Refer Another / Withdrawn Consent, Refer Another / Not entered)

h. Result (Cancer Detected / High-risk Adenoma / Intermediate-Risk adenoma / Low-risk Adenoma / Abnormal / Abnormal, procedure incomplete / Normal (No Abnormalities Found) / No Result)

i. Outcome of result (Investigation Complete / Refer Surveillance (BCSP) / Complete – Refer Another / Incomplete – Refer Another / Consent Refused, Refer Another / Withdrawn Consent, Refer Another / Refer Colonoscopy / Refer to MDT / Refer to Surgery / Did Not Attend / Cancelled)

5. Endoscopic Test Table

a. Subject_ID

b. Episode_ID

c. Diag_Test_ID

d. Bowel_Prep (Good / Adequate / Poor)

e. Extent (Ileum / Anastomosis / Appendix / Caecum / Ascending colon / Hepatic flexure / Transverse colon / Splenic flexure / Descending colon / Sigmoid colon / Recto/Sigmoid / Rectum / Anus)

f. Retroversion (Yes / No)

g. Cancer_Exist (Yes / No)

h. Polyp_Exist (Yes / No)

6. Radiology Test Table

a. Subject_ID

b. Episode_ID

c. Diag_Test_ID

d. Bowel_Prep (Good / Adequate / Poor / Not applicable / blank)

e. Diagnosis (Abnormal radiologic density, irregular / Abnormal radiologic density, rounded / Abnormal radiologic density, small area / Benign Submucosal Lesion / Diverticulitis / Diverticulosis / Filling defect / Filling defect - polyp / Filling defect – possible cancer / Fistula / Inflammatory bowel disease / Post-operative appearance / Stricture / Unknown cause)

f. Location (Ileum / Appendix / Caecum / Ascending colon / Hepatic flexure / Transverse colon / Splenic flexure / Descending colon / Sigmoid colon / Recto/Sigmoid / Rectum / Anus / Right colon / Left colon / Entire colon / Patchy areas)

7. Polyps Table

a. Subject_ID

b. Episode_ID

c. Diag_Test_ID

d. Polyp_ID (note this is unique to the specific Diag_Test_ID. Therefore, if the same polyp is documented at multiple Diagnostic Tests, then a new Polyp_ID will be used at each Diagnotic Test)

e. Endoscopic_Size (mm)

f. Location (Ileum / Anastomosis / Appendix / Caecum / Ascending colon / Hepatic flexure / Transverse colon / Splenic flexure / Descending colon / Sigmoid colon / Recto/Sigmoid / Rectum / Anus)

g. Class (Sessile polyp / Pedunculated polyp / Flat polyp / SEMI-PEDUNCULATED (Isp) / FLAT – slightly elevated (IIa) / FLAT – completely flat (IIb) / FLAT – depressed (IIc) / FLAT – slightly elevated with depressed centre (IIa/c) / FLAT – laterally-spreading type, granular (LST-G) / FLAT – laterally-spreading type, non-granular (LST-NG))

h. Removal (En bloc / Piecemeal / Blank)

i. Device (Hot snare / Cold snare / Cold biopsy forceps / Hot biopsy forceps / Injection / Argon beam / Laser / Endoclip / Heater probe / Coagulation grasper / Cannula / Band ligator / Endoscopic knife)

j. Modality (Polypectomy / Mucosal resection (EMR) / Submucosal dissection (ESD) / Biopsy / Tattooing / Haemostatic technique / Chromoscopy / Submucosal lift / Tissue destruction)

k. Histology_Size (mm)

l. Histology_ID (note that more than one Histology_ID may exist for one Polyp_ID)

m. Type (Adenoma / Serrated lesion / Serrated polyp / Inflammatory polyp / Juvenile polyp / Lymphoid polyp / Peutz-Jeghers polyp / Other polyp / Not polyp / Blank)

n. Architecture (Tubulovillous adenoma / Tubular adenoma / Villous adenoma / Hyperplastic / Mixed HP/adenoma / Mixed polyp / Sessile serrated lesion / Sessile serrated lesion with dysplasia / Serrated adenoma / Traditional serrated adenoma / Lipoma / Stromal / Endocrine Tumour (Carcinoid) / Lymphoid / Other polyp / Not reported)

o. Dysplasia (Low grade dysplasia / High grade dysplasia / No dysplasia / Not reported)

p. Excision (Not Assessable / Yes / No / Not Known)

q. Lymphovascular_Invasion (BLANK field)

r. Carcinoma (Yes / No / Uncertain)

s. Polyps_Resected (1 / 0)
t. Polyps_Retrieved (1 / 0)

8. Cancer Table
a. Subject_ID
b. Episode_ID
c. Cancer_ID
d. Type (Tumour – exophytic (Non-ulcerated locally advanced tumour protruding into lumen) / Tumour – annular/stenosing (Circumferential or near-circumferential locally advanced tumour) / Tumour – ulcerated (Ulcerated locally advanced tumour) / Polypoid mass / Minimally elevated tumour / Malignant tumour / Non obstructing lumen / Annular tumour / Obstructing lumen (incomplete or complete) / Saddle Shaped tumour / Stricturing tumour / Submucosal tumour / Blank)
e. Location (Appendix / Caecum / Ascending colon / Hepatic flexure / Transverse colon / Splenic flexure / Descending colon / Sigmoid colon / Recto/Sigmoid / Rectum / Anus)
f. Excision_Type (RESECTION / LOCAL EXCISION / NONE / BLANK)
g. Primary_Procedure (Right Hemicolectomy / Extended right hemicolectomy / Left Hemicolectomy / Sigmoid colectomy / Transverse colectomy / Hartmann's procedure / Anterior resection / Abdominoperineal resection of rectum / Total Colectomy and ileorectal anastomosis / Total excision of colon and rectum / Transanal endoscopic microsurgery / Endoscopic mucosal resection / Polypectomy Endoscopic extirpation of lesion of lower bowel using fibreoptic sigmoidoscope / Snare polypectomy / OTHER / Blank)
h. Treatment_Intent (Curative / Palliative / Uncertain / Blank)
i. Final_pre-treat_T (T1 / T2 / T3 / T4 / Tx)
j. Final_pre-treat_N (N0 / N1 / N2)
k. Final_pre-treat_M (M0 – No Metastases / M1 – Metastases)
l. Pathological Dukes (A / B / C1 / C2)
m. Date_Diagnosis

Following initial exploration of the data and further discussion with the PHE Screening Team, a refreshed data extract of the Cancer Table (Table 8 above) was received and additional data fields were requested and received as follows:

9. Secondary Piece
a. SUBJECT_EPIS_ID (=Episode_ID above)
b. SCREENING_SUBJECT_ID (=Subject_ID above)
c. EXT_TEST_ID (=Diag_Test_ID above)
d. POLYP_ID
e. POLYP_HISTOLOGY_ID (=Histology_ID above)

f. POLYP_W_GTR_1_HISTOLOGY_REC (1 / 0; identifies Polyp_IDs for which there exist >1 Histology_ID)

g. Secondary Piece (Yes / No / blank; identifies Polyp_IDs referring to a second or subsequent histology specimen of a previously reported polyp)

10. Cancer data (from NCRAS)

a. Subject_ID

b. DIAGDATE

c. SITE_CODED_DESC (Appendix / Caecum / Ascending colon / Hepatic flexure of colon / RIGHT COLIC FLEXURE / Transverse colon / Splenic flexure of colon / Descending colon / SIGMOID COLON / Rectosigmoid junction / Rectum NOS / Colon NOS)

d. SITE_CODED_3CHAR (C18 / C19 / C20 / T67)

e. CODING_SYSTEM_DESC (ICD-O-3 (2011) / ICD-10/O-3 / ICD-10/O-2 / SNOMED/O-3)

f. HISTOLOGY_CODED_DESC (Adenocarcinoma, NOS / Adenocarcinoma in villous adenoma / Adenocarcinoma in tubulovillous adenoma / Adenocarcinoma in adenomatous polyp / ADENOCA IN ADENOMATOUS POLYP / Tubular adenocarcinoma / CARCINOMA / Mucinous adenocarcinoma / NEOPLASM MALIGNANT)

g. DUKES (A / B / C1 / C2 / D)

h. T_BEST (1 / 2 / 3 / 4 / 3b / 4a / 4b)

i. N_BEST (0 / 1 / 2 / 2b)

j. M_BEST (0 / 1 / X)

k. STAGE_BEST_SYSTEM (20 / 22 / 24)

l. T_PATH (0 / 1 / 2 / 3 / 4 / 4b)

m. N_PATH (0 / 1 / 2 / 2b / X)

n. M_PATH (0 / 1 / X)

o. STAGE_PATH (2)

1.2. Personal details formatting

- PDEpisode_ID1
  - Height_m1
  - Weight_kg1
  - Alcohol1
  - Alcohol_UnitsWeek1
  - Smoker1
  - ASAgrade1

And continued up to:

- PDEpisode_ID6
  - Height_m6
  - Weight_kg6
  - Alcohol6
  - Alcohol_UnitsWeek6
  - Smoker6
  - ASAgrade6

1.3. Surveillance episode

- SuEpisode_ID1
- SuAge_Epi_Start1
- SuEpisode_Result1

And for each diagnostic test within each surveillance episode:

- SuDiag_Test_ID1_1
- SuTest_Date1_1
- SuTest_Type1_1
- SuBowel_Prep1_1
- SuExtent1_1

For the second diagnostic test within the first surveillance episode for that individual subject:

- SuDiag_Test_ID1_2
- SuTest_Date1_2
- SuTest_Type1_2
- SuBowel_Prep1_2
- SuExtent1_2

And continued up to:

- SuDiag_Test_ID5_7
- SuTest_Date5_7
- SuTest_Type5_7
- SuBowel_Prep5_7
- SuExtent5_7

1.4. Deriving Analysis Variables

In order to allow analysis in Stata, further variables were created as detailed below.

Age

Age_grp_final – derived from Screen_Test_Date (i.e. date of first diagnostic test in the subject's screening episode)

1 – <65

2 – 65-69

3 – >69

BMI

Height_final – the first documented height found in the Personal Details variables. If Height_m1 is not blank, then this value populates Height_final. Where Height_m1 is blank, Height_m2 populates Height_final, and so on to Height_m6.

- If Height_final ≥2m or <1.4m, then the Height_m values were reviewed as there was a likelihood of data entry error. Where a more plausible Height_m existed, this was used to overwrite Height_final. A total of 8 subjects had Height_final overwritten by this process.

Weight_final – the first documented weight found in the Personal Details variables. If Weight_kg1 is not blank, then this value populates Weight_final. Where Weight_kg1 is blank, Weight_kg2 populates Weight_final, and so on to Weight_kg6.

- If Weight_final >150kg or <36kg, then the Weight_kg values were reviewed as there was a likelihood of data entry error. Where a more plausible Weight_kg existed, this was used to overwrite Weight_final. A total of 22 subjects had Weight_final overwritten by this process.

BMI – calculated as Weight_final/(Height_final)2

- After review of the Weight_final and Height_final values at the upper and lower extremes of BMI, it was decided to accept a BMI of between 10 and 90 as plausible and retain these BMI values. All other BMIs were coded as missing. (There were 31 subjects with a BMI value <10 or >90, where both a Weight_final and Height_final value existed, but the BMI result was overwritten as "missing" by this process.)

BMI_grp – based on BMI, where:

1 – BMI of ≥12 and <18.5

2 – BMI of ≥18.5 and <25

3 – BMI of ≥25 and BMI <30

4 – BMI of ≥30 and BMI <40

5 – BMI of ≥40 and BMI ≤90
9 – BMI <12 OR >90 OR "0" OR "."

Alcohol
Alcohol_final – the first documented Alcohol_UnitsWeek. Where no value is documented in any of the six Alcohol_UnitsWeek fields, Alcohol_final is coded as a missing field (includes cases where no Alcohol field contains "Yes").

Smoking
Smoker_final – the first documented value in a Smoker field, coded as:
0 – No
1 – Yes
2 – Ex-smoker
9 – all 6 Smoker fields blank

ASA grade
ASA_final – the first documented ASA grade (1 to 5) in the personal details fields. Where no ASA grade exists in any of the six ASAgrade fields, ASA_final is coded as missing (=9).

Colonoscopy as the first diagnostic test in the episode
Col_first – based on the screening episode, where:
0 – first diagnostic test is not a colonoscopy
1 – first diagnostic test is a colonoscopy
SuX_Col_first – X = 1 to 5 corresponding to each surveillance episode, where:
0 – first diagnostic test is not a colonoscopy
1 – first diagnostic test is a colonoscopy
9 – no surveillance episode at that numeric position

No colonoscopy in an episode
No_Col – based on the screening episode, where:
0 – colonoscopy performed at any time in the episode
1 – no colonoscopy exists within the episode
SuX_No_Col – X = 1 to 5 corresponding to each surveillance episode, where:
0 – colonoscopy performed at any time in the episode
1 – no colonoscopy exists within the episode
9 – no surveillance episode at that numeric position

Multiple diagnostic tests in an episode
Multi_Tests – based on the screening episode, where:
0 – only one diagnostic test (of any type) in the episode

1 – more than one diagnostic test (of any type) in the episode

SuX_Multi_Tests – X = 1 to 5 corresponding to each surveillance episode, where:

0 – only one diagnostic test (of any type) in the episode

1 – more than one diagnostic test (of any type) in the episode

9 – no surveillance episode at that numeric position

Colonoscopy quality – Extent of examination

extentX_final – extent of colonoscopy in the corresponding numeric position (X = 1 to 9) within the screening episode, where:

1 – "caecum" OR "ileum" OR "appendix" OR "anastomosis"

0 – any other extent

Col_incomplete – coded as:

0 – at least one colonoscopy within the screening episode where extent_final = 1

1 – no colonoscopy within the screening episode has extent_final = 1

2 – no colonoscopy exists within the screening episode (i.e. No_Col = 1)

SuX_X_extent_final – extent of colonoscopy in the corresponding numeric position (X = 1_1 to 5_7) within the surveillance episode (1 to 5), where:

1 – "caecum" OR "ileum" OR "appendix" OR "anastomosis"

0 – any other extent

SuX_max_extent – (X = 1 to 5) coded as:

0 – no colonoscopy within the surveillance episode has SuX_X_extent_final = 1

1 – at least one colonoscopy within the surveillance episode where SuX_X_extent_final = 1

2 – no colonoscopy exists within that surveillance episode (i.e. SuX_No_Col = 1)

Colonoscopy quality – Bowel preparation

Poor_Prep – based on the screening episode, where:

0 – Complete colonoscopy with "adequate" or "good" prep

1 – Complete colonoscopy with "poor" prep

2 – Incomplete colonoscopy (i.e. Col_incomplete = 1)

3 – no colonoscopy in that episode (i.e. No_Col = 1)

SuX_Poor_Prep – X = numeric position of corresponding surveillance episode:

0 – Complete colonoscopy with "adequate" or "good" prep

1 – Complete colonoscopy with "poor" prep

2 – Incomplete colonoscopy (i.e. SuX_max_extent = 0)

3 – no colonoscopy in that episode (i.e. SuX_No_Col = 1)

Surveillance interval

SuX_1date – the date of the first diagnostic test within the corresponding surveillance episode (X = 1 to 5), based on SuTest_DateX_1.
Su_int1 – interval in days between Screen_Test_Date and Su1_1date
Su_int2 – interval in days between Su1_1date and Su2_1date
Su_int3 – interval in days between Su2_1date and Su3_1date
Su_int4 – interval in days between Su3_1date and Su4_1date
Su_int5 – interval in days between Su4_1date and Su5_1date

Su_intX_grp – based on Su_intX, where:
0 – surveillance interval of <270 days (9m)
1 – surveillance interval of ≥270 days (9m) AND <550 days (18m)
2 – surveillance interval of ≥550 days (18m) AND <900 days (2.5y)
3 – surveillance interval of ≥900 days (2.5y) AND <1460 days (4y)
4 – surveillance interval of ≥1460 days (4y)
9 – MISSING

Episode result
SuX_Epi_Result coded the episode result for each surveillance episode (X = 1 to 5) in a numeric form (with labels) as follows:
1. Abnor-No-Histology
2. Abnormal
3. Blank
4. Cancer
5. High-Risk
6. Int-Risk
7. Low-Risk
8. No-Result
9. Normal

1.5. Blank surveillance episodes

The analysis variables to be "shuffled" left were:
- SuX_No_Col
- SuX_Col_first
- SuX_Multi_Tests
- SuX_max_extent
- SuX_Poor_Prep
- SuX_Epi_Result

The following .do file (based on SuX_No_Col) was modified for each of the above variables:

*FIRST EVER Su_Episode SHUFFLED TO Su1_No_Col

*Su1_exists==0

replace Su1_No_Col=Su2_No_Col if Su1_exists==0

replace Su2_No_Col=Su3_No_Col if Su1_exists==0

replace Su3_No_Col=Su4_No_Col if Su1_exists==0

replace Su4_No_Col=Su5_No_Col if Su1_exists==0

replace Su5_No_Col=9 if Su1_exists==0

*Su1_exists==0 & Su2_exists==0

replace Su1_No_Col=Su2_No_Col if Su2_exists==0 & Su1_exists==0

replace Su2_No_Col=Su3_No_Col if Su2_exists==0 & Su1_exists==0

replace Su3_No_Col=Su4_No_Col if Su2_exists==0 & Su1_exists==0

replace Su4_No_Col=9 if Su2_exists==0 & Su1_exists==0

*Su1_exists==0 & Su2_exists==0 & Su3_exists==0

replace Su1_No_Col=Su2_No_Col if Su3_exists==0 & Su2_exists==0 & Su1_exists==0

replace Su2_No_Col=Su3_No_Col if Su3_exists==0 & Su2_exists==0 & Su1_exists==0

replace Su3_No_Col=9 if Su3_exists==0 & Su2_exists==0 & Su1_exists==0

*Su1_exists==0 & Su2_exists==0 & Su3_exists==0 & Su4_exists==0

replace Su1_No_Col=Su2_No_Col if Su4_exists==0 & Su3_exists==0 & Su2_exists==0 & Su1_exists==0

replace Su2_No_Col=9 if Su4_exists==0 & Su3_exists==0 & Su2_exists==0 & Su1_exists==0

*Su1 EXISTS BUT SUBSEQUENT GAP

*Su2_exists==0

replace Su2_No_Col=Su3_No_Col if Su1_exists==1 & Su2_exists==0

replace Su3_No_Col=Su4_No_Col if Su1_exists==1 & Su2_exists==0

replace Su4_No_Col=Su5_No_Col if Su1_exists==1 & Su2_exists==0

replace Su5_No_Col=9 if Su1_exists==1 & Su2_exists==0

*Su2_exists==0 & Su3_exists==0

replace Su2_No_Col=Su3_No_Col if Su1_exists==1 & Su2_exists==0 & Su3_exists==0

replace Su3_No_Col=Su4_No_Col if Su1_exists==1 & Su2_exists==0 & Su3_exists==0

replace Su4_No_Col=9 if Su1_exists==1 & Su2_exists==0 & Su3_exists==0

*Su2_exists==0 & Su3_exists==0 & Su4_exists==0

replace Su2_No_Col=Su3_No_Col if Su1_exists==1 & Su2_exists==0 & Su3_exists==0 & Su4_exists==0

replace Su3_No_Col=9 if Su1_exists==1 & Su2_exists==0 & Su3_exists==0 & Su4_exists==0

*Su2 EXISTS BUT SUBSEQUENT GAP

*Su3_exists==0

replace Su3_No_Col=Su4_No_Col if Su1_exists==1 & Su2_exists==1 & Su3_exists==0

replace Su4_No_Col=Su5_No_Col if Su1_exists==1 & Su2_exists==1 & Su3_exists==0

replace Su5_No_Col=9 if Su1_exists==1 & Su2_exists==1 & Su3_exists==0

*Su3_exists==0 & Su4_exists==0

replace Su3_No_Col=Su4_No_Col if Su1_exists==1 & Su2_exists==1 & Su3_exists==0 & Su4_exists==0

replace Su4_No_Col=9 if Su1_exists==1 & Su2_exists==1 & Su3_exists==0 & Su4_exists==0

*Su3 EXISTS BUT SUBSEQUENT GAP

*Su4_exists==0

replace Su4_No_Col=Su5_No_Col if Su1_exists==1 & Su2_exists==1 & Su3_exists==1 & Su4_exists==0

replace Su5_No_Col=9 if Su1_exists==1 & Su2_exists==1 & Su3_exists==1 & Su4_exists==0

*Su1 MISSING BUT Su2 EXISTS WITH SUBSEQUENT FURTHER GAP

*Su3_exists==0

replace Su2_No_Col=Su3_No_Col if Su1_exists==0 & Su2_exists==1 & Su3_exists==0

replace Su3_No_Col=Su4_No_Col if Su1_exists==0 & Su2_exists==1 & Su3_exists==0

replace Su4_No_Col=9 if Su1_exists==0 & Su2_exists==1 & Su3_exists==0

*Su3_exists==0 & Su4_exists==0

replace Su3_No_Col=Su4_No_Col if Su1_exists==0 & Su2_exists==1 & Su3_exists==0 & Su4_exists==0

replace Su4_No_Col=9 if Su1_exists==0 & Su2_exists==1 & Su3_exists==0 & Su4_exists==0

*Su1 MISSING BUT Su2 & Su3 EXISTS WITH SUBSEQUENT FURTHER GAP in Su4

replace Su3_No_Col=Su4_No_Col if Su1_exists==0 & Su2_exists==1 & Su3_exists==1 & Su4_exists==0

replace Su4_No_Col=9 if Su1_exists==0 & Su2_exists==1 & Su3_exists==1 & Su4_exists==0

*Su1 EXISTS, Su2 MISSING, Su3 EXISTS, Su4 MISSING

replace Su3_No_Col=Su4_No_Col if Su1_exists==1 & Su2_exists==0 & Su3_exists==1 & Su4_exists==0

replace Su4_No_Col=9 if Su1_exists==1 & Su2_exists==0 & Su3_exists==1 & Su4_exists==0

Su_intX

The above process was also required for the surveillance interval variable, Su_intX. However, this procedure was modified as the interval can be calculated only where two consecutive episode dates exist. Therefore, the following .do file was created for this purpose:

*SORT Su_int1 FIRST

replace Su_int1= Su2_1date- Screen_Test_Date if Su1_exists==0

replace Su_int1= Su3_1date- Screen_Test_Date if Su1_exists==0 & Su2_exists==0

*Su1 EXISTS BUT SUBSEQUENT GAP

*Su2_exists==0

replace Su_int2= Su3_1date- Su1_1date if Su1_exists==1 & Su2_exists==0

*Su2_exists==0 & Su3_exists==0

replace Su_int2= Su4_1date- Su1_1date if Su1_exists==1 & Su2_exists==0 & Su3_exists==0

*Su2 EXISTS BUT SUBSEQUENT GAP

*Su3_exists==0

replace Su_int3= Su4_1date- Su2_1date if Su1_exists==1 & Su2_exists==1 & Su3_exists==0

replace Su_int4= Su5_1date- Su4_1date if Su1_exists==1 & Su2_exists==1 & Su3_exists==0 & Su4_exists==1

*Su3 EXISTS BUT SUBSEQUENT GAP

*Su4_exists==0

replace Su_int4= Su5_1date- Su3_1date if Su1_exists==1 & Su2_exists==1 & Su3_exists==1 & Su4_exists==0

*Su1 MISSING BUT Su2 EXISTS WITH SUBSEQUENT FURTHER GAP

*Su3_exists==0

replace Su_int2= Su4_1date- Su2_1date if Su1_exists==0 & Su2_exists==1 & Su3_exists==0

replace Su_int3= Su5_1date- Su4_1date if Su1_exists==0 & Su2_exists==1 & Su3_exists==0

*Su1 MISSING BUT Su2 & Su3 EXISTS

replace Su_int2= Su3_1date- Su2_1date if Su1_exists==0 & Su2_exists==1 & Su3_exists==1

replace Su_int3= Su4_1date- Su3_1date if Su1_exists==0 & Su2_exists==1 & Su3_exists==1 & Su4_exists==1

replace Su_int4= Su5_1date- Su4_1date if Su1_exists==0 & Su2_exists==1 & Su3_exists==1 & Su4_exists==1 & Su5_exists==1

*Su1 MISSING BUT Su2 & Su3 EXISTS WITH SUBSEQUENT FURTHER GAP in Su4

replace Su_int3= Su5_1date- Su3_1date if Su1_exists==0 & Su2_exists==1 & Su3_exists==1 & Su4_exists==0

*Su1 EXISTS, Su2 MISSING, Su3 EXISTS

replace Su_int3= Su4_1date- Su3_1date if Su1_exists==1 & Su2_exists==0 & Su3_exists==1 & Su4_exists== 1

replace Su_int4= Su5_1date- Su4_1date if Su1_exists==1 & Su2_exists==0 & Su3_exists==1 & Su4_exists== 1

replace Su_int3= Su5_1date- Su3_1date if Su1_exists==1 & Su2_exists==0 & Su3_exists==1 & Su4_exists== 0

*Su_int TO MISSING IF PRECEDING GAPS

replace Su_int3=9999 if Su_count==2

replace Su_int4=9999 if Su_count==2 | Su_count==3

replace Su_int5=9999 if Su_count==2 | Su_count==3 | Su_count==4

1.6. Polyp data cleaning

The following plan for data cleaning was formulated in order to deal with these various scenarios:

Field	**Rule**	**Rationale**	**Comments**
Endoscopic_Size	Exclude size of ≥100mm	Likely data entry error	Polyp should still be counted – as >10mm
Histology_Size	Exclude size of ≥100mm	Likely data entry error	Polyp should still be counted – as >10mm
Location	Exclude "anus" / "anastomosis" / "ileum"	These are not colorectum	
Location	"appendix"	Include as "caecum"	
Carcinoma	Exclude patient if "yes"	Surveillance after a polyp cancer higher risk group than HR(?)	
Carcinoma	Include if "uncertain"	These are likely to be HGD (+/- "IMCa")	
Modality	Exclude tissue destruction	APC used at EMR edges	

Modality	Exclude Tattooing	Additional row (*usually* refers to polypectomy)	This will exclude lesions sent for benign surgery, so exclude only if endo resection also performed
Modality	Exclude Biopsy	Likely polypectomy will be performed at later colonoscopy	This will exclude lesions sent for benign surgery, so exclude only if endo resection also performed
Modality	Exclude Haemostatic technique	Additional row (refers to polypectomy)	
Modality	Exclude submucosal lift	Additional row (refers to polypectomy)	
Modality	Exclude chromoscopy	Additional row (refers to polypectomy)	

Table 65 – Polyp data exclusion criteria

Field	**Rule**	**Rationale**	**Comments**
Class	Reclassify as: 1. pedunculated 2. sessile 3. flat 4. LST-NG 5. LST-G		Could combine to binary "pedunculated" / "non-pedunculated" later
Location	Summarise as caecum (N), rectum (N), proximal (N)	No evidence of differing risk between further subclassified lesions	Splenic flexure as threshold for proximal (SF being distal). Rectosigmoid as sigmoid.

Table 66 - Consolidating polyp data for analysis

Episode 1							
	Adenomas						
Date (earliest)	N total	Largest size (mm)	Piecemeal	NTA	NTVA	NVA	NHGD
	x	x	y/n	x	x	x	x

Adenomas (continued)								
Location			Morphology (adenomas ≥10mm)					
N proximal	N rectal	N caecal	N ≥10mm total	N ≥10mm pedunculated	N ≥10mm sessile	N ≥10mm flat	N ≥10mm LST-G	N ≥10mm LST-NG
X	x	x	x	x	x	x	x	x

Serrated						
					Location	
N total	Largest size (mm)	Piecemeal	NHGD	NLGD	N proximal	N rectal
X	x	y/n	x	x	x	x

Table 67 - Polyp details for analysis

Counting polyps

The PHE Screening Team provided the current rules used in the BCSS algorithm to determine when a polyp is counted as an adenoma. The following processes occur in BCSS:

Adenoma definition

A polyp is included in the adenoma count ONLY if one of the following is true, the algorithm should be applied in the order stated:

1. 'Secondary piece of polyp already partially removed' not=Yes AND

2. Any intervention of polypectomy, EMR or ESD is associated with the polyp AND

a) Histology 'polyp type'='Adenoma' OR

b) Histology 'polyp type'='Serrated Lesion' AND Histology 'polyp sub type'=Serrated adenoma (historic) OR

c) Histology 'polyp type'=Serrated Lesion AND Histology 'polyp sub type'=Mixed HP/Adenoma (historic) OR

d) Histology 'polyp type'=Serrated Lesion AND Histology 'polyp sub type'=Sessile serrated lesion with dysplasia OR

e) Histology 'polyp type'=Serrated Lesion AND Histology 'polyp sub type'=Traditional serrated adenoma OR

f) Histology 'polyp type'=Serrated Lesion AND Histology 'polyp sub type'=Mixed polyp OR

1. 'Secondary piece of polyp already partially removed' not=Yes AND

2. There is no histology associated with an intervention 'modality' of (EMR, polypectomy, ESD)

AND

3. an intervention 'modality' of polypectomy, EMR or ESD is associated with the polyp AND

4. intervention 'excised' ='yes' AND intervention 'retrieved'=No

OR

1. 'Secondary piece of polyp already partially removed' not=Yes(OR doesn't exist) AND

2. There is no histology associated with intervention 'modality' of (EMR, polypectomy, ESD) AND

3. An intervention 'modality' of Tissue destruction is associated with the polyp

OR

1. 'Secondary piece of polyp already partially removed' not=Yes AND

a. Pathology lost='yes'

NOTES

- "Resected" (0 / 1) has been used since 30/03/2011 so that Resected must = 1 for a polyp to be counted as an adenoma. Note:

o Since 30/03/2011, there are approximately 430 "biopsies" and a further 150 "EMR" or "polypectomy" where resected = 0 AND size ≤5mm. It is likely that these small lesions were in fact resected, but not counted according to the BCSS algorithm.

o Before 30/03/2011, there are approximately 3430 "biopsies" and a further 1780 "EMR" or "polypectomy" where resected = 0 AND size ≤5mm.

o There approximately 450 adenomas with "Blank" modality, resected = 0. Of these, 180 are ≤5mm and so likely were in fact resected.

- "Secondary piece" (all since Jan 2008)

o 1105 of these (<1105 polyps, as there may be >1 secondary piece for a single polyp)

- Approximately 460 unique polyps have >1 histology result (noted in the Secondary Piece data extract)

In the original Polyp_Table (3/1/2017 extract), there are

- 276854 rows where resected = 1 AND modality is either "polypectomy", "EMR" or "ESD"
- Where resected = 0:

o 1861 "tissue destruction" where size >5mm (ACCEPT AS NOT RESECTED if only entry for that Polyp_ID)

o 1315 "tissue destruction" where size ≤5mm (COUNT AS IF RESECTED) – many are hot biopsy & have histology

o 4138 "polypectomy", "EMR" or "ESD" as modality (of these 2000 are of ≤5mm size, so likely WERE resected). (COUNT AS IF RESECTED BASED ON SIZE)

Plan

In Excel

1. Delete row if MODALITY (column J) = submucosal lift / chromoscopy / haemostatic technique
2. Delete row if TYPE (column M) = Peutz-Jeghers / Other polyp / not polyp / lymphoid / juvenile / inflammatory
3. Delete row if LOCATION = anus / anastomosis / ileum
4. If >1 Histo_ID, then review individually to ensure most complete data kept (i.e. is associated with polypectomy (OR biopsy OR tissue destruction) row
5. Then individually review (54) polyps where (either endo or histo) size ≥100mm

a. RULES:

i. If either size <100mm, THEN overwrite size (e.g. pedunculated polyp of 12mm histo size where endo size=112)

In STATA

1. Drop

a. Histo_ID – not required

b. lymphovasc invasion (blank field)

c. Ca_exists (as unreliable – using NCRAS validated Ca data)

d. excision (completeness) – unreliable (e.g. piecemeal resection)

2. finddup Polyp_ID – Stata command to identify and number multiple rows associated with a single Polyp_ID.

3. generate "size" variable (histo > endo except where Piecemeal – then endo > histo)

4. generate "histology" variable (architecture > type)

5. drop:

a. endo size

b. histo size

c. type

d. architecture

6. reshape wide on Polyp_ID

7. If Secondary Piece, then

a. Retain highest risk features: HGD or villous if present in any piece

b. Mark retained Polyp_ID to flag "secondary piece" (as "primary piece")

c. Disregard secondary piece IF not same histology type as original specimen: adenoma OR serrated (i.e. "unmark" as secondary piece – this is a different polyp as different histology)

8. Drop: (Below variables are consistent across the sets of data per Polyp_ID. Therefore, histology1, dysplasia1, location1, and class1 will be used.)

a. histology2/3/4

b. dysplasia2/3/4

c. location2/3/4

d. class2/3/4

9. Select size

- Up to four size entries exist per Polyp_ID (size1/2/3/4). The largest of these will be used and others dropped.

10. Select modality:

- ESD > EMR > polypectomy > biopsy > tissue destruction > tattooing

11. Where resected = 0:

- If size ≤5mm AND (biopsy OR tissue destruction), THEN count as resected

12. Count if resected = 1 in ANY position for that Polyp_ID OR PrimaryPiece = 1 (as resected may have = 1 in the deleted SecondaryPiece)

13. gen location_group:

a. "rectum" if rectum OR rectosigmoid

b. "proximal" if ascending OR hepatic flexure OR transverse

c. "caecum" if caecum OR appendix

d. "distal" if splenic flexure OR descending OR sigmoid

14. Flags for:

a. Biopsy = polypectomy (follows 11 above)

b. No resection of a "large" (>5mm) polyp

[Note for larger (≥20mm) polyps, it is possible that a resection occurred outside the BCSP (endoscopic or surgical). To enter surveillance, it is assumed that all detected adenomas have been resected.]

c. Tattoo exists

d. (+ retain Resected = 0)

15. merge above Polyp Stata file to existing screen & surv Stata file on Episode_ID

16. If Multi_Tests / SuX_Multi_Tests = 1:

a. Polyps reported at an endoscopic test are used and any preceding radiology [CTC] test disregarded.

b. AND Poor_Prep / SuX_Poor_Prep = 1 OR 2 OR 3, then polyps at a subsequent (radiology [CTC]) test can be ADDED (and marked to indicate if there is no documentation of resection).

c. (Ba enema / Abdo CT / Scan (x-ray) – discounted)

17. Then individually review (<110) cases where ≥20 polyps exist in one Episode_ID

18. generate analysis variables PER EPISODE (screen & surv):

a. ALL adenomas

i. n

ii. largest (mm)

iii. piecemeal Y/N

iv. n TA

v. n TVA

vi. n VA

vii. n HGD

viii. n LGD

ix. n proximal

x. n rectum

xi. n caecum

xii. n distal

b. Adenomas ≥10mm

i. n

ii. n pedunculated

iii. n sessile

iv. n flat

v. n LST-G

vi. n LST-NG

c. Serrated

i. n

ii. largest (mm)

iii. piecemeal Y/N
iv. n HGD
v. n LGD
vi. n proximal
vii. n rectum
viii. n caecum
ix. n distal

APPENDIX 2

Publications arising from this thesis

World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
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EDITORIAL

Surveillance of colonic polyps: Are we getting it right?

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Abstract

Colorectal cancer (CRC) is the third most commonly diagnosed cancer worldwide. The identification of colonic polyps can reduce CRC mortality through earlier diagnosis of cancers and the removal of polyps: the precursor lesion of CRC. Following the finding and removal of colonic polyps at an initial colonoscopy, some patients are at an increased risk of developing CRC in the future. This is the rationale for post-polypectomy surveillance colonoscopy. However, not all individuals found to have colonic adenomas have a risk of CRC higher than that of the general population. This review examines the literature on post-polypectomy surveillance including current international clinical guidelines. The potential benefits of surveillance procedures must be weighed against the burden of colonoscopy: resource use, the potential for patient discomfort, and the risk of complications. Therefore surveillance colonoscopy is best utilised in a selected group of individuals at a high risk of developing cancer. Further study is needed into the specific factors conferring higher risk as well as the efficacy of surveillance in mitigating this risk. Such evidence will better inform clinicians and patients of the relative benefits of colonoscopic surveillance for the individual. In addition, the decision to continue with surveillance must be informed by the changing profile of risks and benefits of further procedures with the patient's advancing age.

Key words: Adenoma; Polyp; Colonoscopy; Surveillance; Colorectal cancer

Core tip: Increasing numbers of surveillance colonoscopies for previous colonic polyps are being performed. Each colonoscopy brings the burden of bowel preparation, potential discomfort, and risk of complications. Colonoscopy is a finite resource and must be recommended only with a strong indication. Individuals with non-advanced adenomas have no significantly increased risk of colorectal cancer (CRC) compared to the general population. Patients with an advanced adenoma, have a CRC risk similar to that of the general population after just one surveillance colonoscopy. This review examines the evidence behind

current surveillance guidelines and questions the rationale for surveillance in individuals with relatively low cancer risk.

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INTRODUCTION

Colorectal cancer (CRC) is the second leading cause of death from cancer in the United Kingdom[1] and United States[2]. Over 41000 people in the United Kingdom are diagnosed with CRC annually and over 16000 people die of the disease.

Recognised risk factors for the development of CRC include advancing age, a personal or family history of CRC, longstanding inflammatory bowel disease affecting the colon, and specific conditions such as familial adenomatous polyposis (FAP), and hereditary non-polyposis colon cancer (HNPCC). This review focuses on an important risk factor for the development of CRC: a personal history of colorectal adenomas.

Some colonic polyps such as adenomatous and serrated polyps carry malignant potential, while others do not (hyperplastic, post-inflammatory, hamartomatous). This review will discuss only those polyps with malignant potential.

The majority of CRCs arise from colonic adenomas. Adenomas arise following aberrant proliferation of epithelial cells in the colon. These lesions may then progress to varying degrees in size and dysplasia[3]. Adenomas represent the major precursor for CRC both in high-risk groups such as patients with a family history of familial adenomatous polyposis (FAP) or hereditary non-polyposis colorectal cancer (HNPCC), as well as in the general population. This concept is termed the "adenoma-carcinoma sequence"[4-8].

However, 20%-30% of colorectal cancers arise through a different molecular pathway to the conventional adenoma-carcinoma sequence. These CIMP-positive cancers (CpG island methylator phenotype) are believed to arise from serrated polyps. Such lesions are over-represented among "interval cancers" (cancers diagnosed 6-36 mo after a colonoscopy)[9]. Growing evidence points to the importance of recognising and managing serrated lesions in preventing CRC[10].

The speed of progression along the pathway of proliferation and dysplasia is a key factor in determining clinical practice in patients found to have colonic adenomas. Progression from adenoma to invasive cancer can occur in 5 years or take more than 20 years[11]. Additionally, progression along this pathway is highly variable: one study estimates that only 0.25% of adenomas per year will progress to cancer[12]: some stabilise and some regress[11,13-15].

Adenoma prevalence in Western screening populations (age 50-75 years) can be as high as 40%, with advancing age and male sex associated with higher prevalence. However, lifetime risk of CRC is only 5.5% due to the highly variable progression of adenomas[16-22]. Overall, projections of 10-year cumulative risk for progression from adenoma to carcinoma are less than 10%[15,23].

RISK FACTORS

In recent years, an understanding of adenoma features predicting risk of progression to cancer has led to the term "advanced adenoma"[15], referring to adenomas possessing at least one of three high risk characteristics: size of at least 10 mm, villous architecture of at least 25%, or high grade dysplasia[24-26]. Overall, these lesions progress to cancer at an annual rate of up to 5%: significantly higher than the average rate for all adenomas[12], and this risk increases with age to 25% at age 55 years and to 40% at age 80 years. Annual rates of progression from adenoma to carcinoma also vary depending on which of these advanced features is present. Size of at least 10 mm confers a 3% annual risk; villous architecture 17%, and high grade dysplasia 37%[12].

As these figures illustrate, high grade dysplasia (HGD) confers high risk of progression to cancer. However, in keeping with the adenoma-carcinoma sequence described previously, high grade dysplasia is more likely to be found in larger lesions: as adenomas progress in size, so too dysplasia progresses[27]. The number of adenomas possessing advanced features (HGD or > 25% villous architecture) increases with polyp size from approximately 1%-2% in diminutive adenomas (< 5 mm) to 7%-12% for small adenomas (5-9 mm) and 20%-30% for large adenomas (≥ 10 mm)[24,28,29]. Advancing age of the patient also increases the likelihood of HGD within an adenoma, independent of polyp size and histological type[30].

Most adenomas detected at colonoscopy (60%-75%) are smaller than 10 mm diameter[31]. Larger adenomas of at least 10 mm in diameter are at higher risk of containing CRC and are also a risk factor for metachronous cancer development (*i.e.*, a cancer diagnosed at least 6 mo after the index procedure)[24]. The absolute risk of metachronous advanced adenomas is close to 20% in patients whose largest baseline adenoma is 20 mm or more in size[32].

The risk factor most closely correlating to CRC risk is the total number of adenomas, both at index procedure and cumulatively over the individual's lifetime. Patients with one or two small tubular adenomas removed do not have a significantly increased metachronous colorectal cancer risk[33]. In contrast, the presence of

one or more advanced adenomas predicts a higher rate of both any and advanced metachronous adenomas[25]. The risk of metachronous CRC increases with the number of advanced adenomas[24]. Large polyp size (≥ 10 mm) and proximal location in the colon are independent predictors of further advanced neoplasia at follow-up[34]. The risk for metachronous advanced adenomas increases progressively with the number of adenomas at baseline examination: patients with only 1 adenoma have a risk of 9% while those with 5 or more adenomas have a 24% risk.

BENEFIT OF COLONOSCOPY

Colonoscopic screening has been shown to be effective in reducing CRC incidence and mortality[27,35-38].

This effect is *via* a number mechanisms. Firstly, the removal of pre-cancerous lesions, *i.e.,* adenomatous polyps, thereby interrupting the progression to carcinoma: preventing cancers. Secondly, detection of CRC at an earlier, pre-symptomatic stage with resultant increased likelihood of successful endoscopic or surgical treatment[27,39-41].

The third mechanism, which may reduce CRC incidence and mortality, is surveillance colonoscopy. Risk stratification based upon index colonoscopy findings allows patients with polyps at higher risk of progression to cancer to be offered a further examination in the future[19,20,42]. The evidence for the potential benefits of surveillance will be discussed in detail later.

Patients diagnosed with CRC at an earlier stage have significantly better prognosis than those diagnosed with more extensive disease. Of patients diagnosed with Dukes' A CRC, 93% will survive 5 years. Those diagnosed with modified Dukes' D cancer however, have a less than 7% chance of living a further 5 years.

Colonoscopy is considered to be the gold standard for adenoma detection and affords an opportunity for therapy, through polypectomy, as well as allowing histological diagnosis. Double-contrast barium enema and CT colonography (CTC) show poorer sensitivity compared to colonoscopy, particularly with respect to very small and flat polyps[43,44]. An optimally performed double-contrast barium enema and FIT (faecal immunohistochemical test) detect only half of adenomas of 5 mm or larger that are detected by colonoscopy[45].

LIMITATIONS OF COLONOSCOPY

However, there remain limitations to colonoscopic screening. Even colonoscopy does not allow detection of all adenomas. "Back-to-back" colonoscopies have indicated significant miss rates of 27% for small adenomas (< 5 mm) and 6% for adenomas of more than 10 mm diameter[46]. Studies performing both CTC and colonoscopy estimate that the colonoscopy miss rate for polyps over 10 mm in size may be as high as 12%[47]. There are multiple factors likely to contribute to missed polyps at colonoscopy including quality of bowel preparation, and the training and experience of the colonoscopist. The time taken by colonoscopists during withdrawal of the colonoscope from the caecum is a powerful predictor of adenoma detection rate (ADR)[48]. Higher rates of interval cancers are seen in association with low ADR at screening colonoscopy[49,50].

The protection afforded by colonoscopy is significantly greater in respect of distal CRC as compared to lesions of the proximal colon. There are a number of factors postulated to explain this differential: poorer right-sided bowel preparation, incomplete colonoscopy, anatomical factors impeding visibility, and potentially different biology of right-sided lesions, especially via the serrated pathway[35,51].

Incomplete resection of adenomatous tissue is believed to be a substantial contributor to interval cancers. Rates of incomplete resection for diminutive polyps are 29% for conventional biopsy and 17% for hot biopsy[52,53]. Residual polyp tissue is more likely to remain after resection of sessile polyps and risk increases with polyp size. Rates of 17% for polyps of 10-20 mm and 7% for lesions of 5-9 mm have been quoted. There also appears to be a higher rate of incomplete resection for serrated lesions in comparison to conventional adenomas (31% and 7% respectively)[54].

Missed lesions are likely to account for more than half of interval cancers diagnosed at 3 to 5 years after the index procedure[55]. Therefore, the quality of the index and subsequent colonoscopies is paramount in maximising the potential benefit of surveillance procedures. Quality of colonoscopy is directly associated with rates of interval CRC[50].

RATIONALE FOR SURVEILLANCE

The major CRC mortality risk reduction is achieved at index colonoscopy, *i.e.,* diagnosis of cancers at an earlier stage and removal of adenomas with the aim of reducing CRC incidence.

Individuals found to have colonic polyps are at increased risk of advanced neoplasia in the future[11,23,56,57]. This risk may be due to a number of mechanisms: (1) Missed lesions at the initial colonoscopy; (2) Incomplete removal of adenomatous tissue at initial colonoscopy; and (3) The individual's propensity to colonic neoplasia (either lifestyle factors, an inherent imbalance of cell proliferation, or a combination of these)[25,46,57-60].

In view of the increased risk of CRC, it seems logical that this group may benefit from closer monitoring than the general population. There are two reasons to consider surveillance colonoscopy in patients found to have adenomas at the index procedure. Firstly, as discussed above, there may be missed lesions, particularly small polyps, which may be identified at a subsequent procedure. Secondly, after a time interval,

Table 1 British Society of Gastroenterology guidelines 2010[79], supported by the 2011 guidelines of The National Institute for Health and Care Excellence

Risk of colorectal cancer or advanced adenomas (≥ 1 cm as measured at endoscopy or high-grade dysplasia)
Patients with only one or two small (< 1 cm) adenomas are at low risk, and need no colonoscopic surveillance or 5-yearly until one negative examination then cease surveillance. Recommendation grade: B
Patients with three or four small adenomas or at least one adenoma ≥ 1 cm are at intermediate risk and should be screened 3-yearly until two consecutive examinations are negative. Recommendation grade: B
If either of the following is detected at any single examination (at baseline or follow-up): five or more adenomas, or three or more adenomas at least one of which is ≥ 1 cm, the patient is at high risk and an extra examination should be undertaken at 12 mo before returning to 3-yearly surveillance. Recommendation grade: B
Patients can be offered surveillance until age 75 yr and thereafter continue depending on relative cancer risk and comorbidity. Colonoscopy is likely to be less successful and more risky at older ages. Further, the average lead time for progression of an adenoma to cancer is 10 yr which is of the same order as the average life expectancy of an individual aged 75 yr or older, suggesting that most will not benefit from surveillance. Recommendation grade: B
These guidelines are based on accurate detection of adenomas, otherwise risk status will be underestimated. Patients with a failed colonoscopy, for whatever reason, should undergo repeat colonoscopy or an alternative complete colonic examination. Recommendation grade: B
The site of large sessile adenomas removed piecemeal should be re-examined at 2-3 mo. Small areas of residual polyp can then be treated endoscopically, with a further check for complete eradication in 2-3 mo. India ink tattooing aids recognition of the polypectomy site at follow-up. If extensive residual polyp is seen, surgical resection needs to be considered, or alternatively referral to a colonoscopist with special expertise in advanced polypectomy techniques. If there is complete healing of the polypectomy site, then there should be a colonoscopy at 1 yr, to check for missed synchronous polyps, before returning to 3 yearly surveillance. Recommendation grade: B

Table 2 American Gastroenterological Association 2012[80]

Findings at index procedure	Suggested surveillance interval	Strength of evidence
No polyps/small (< 10 mm) rectosigmoid hyperplastic	10 yr	Moderate
1-2 small (< 10 mm) tubular adenomas	5–10 yr	Moderate
3-10 tubular adenomas	3 yr	Moderate
> 10 adenomas	< 3 yr	Moderate
One tubular adenoma ≥ 10 mm	3 yr	High
One villous adenoma	3 yr	Moderate
Adenoma with high grade dysplasia (HGD)	3 yr	Moderate
Serrated lesions		
Sessile serrated polyp (SSP) < 10 mm with no dysplasia	5 yr	Low
SSP ≥ 10 mm OR with dysplasia OR serrated adenoma	3 yr	Low
Serrated polyposis syndrome	1 yr	Moderate

new lesions may have developed.

Although the risk of developing further adenomas is known, no randomised study has directly assessed the effect of post-polypectomy surveillance on CRC incidence or mortality. The efficacy of surveillance has been assessed by retrospective epidemiological series indicating that patients not entered into a surveillance programme have three- to fourfold greater risk of CRC. However, the increased risk pertains to those found to have advanced adenomas at the index procedure. Individuals with non-advanced adenomas did not have significantly higher risk than the general population[23,60].

It is established that individuals with previously identified adenomas have an increased risk of further adenomas at a follow-up examination. At 4 year interval, 35.5% of patients will again be found to have at least one adenoma, but only 8.6%-12% will have advanced neoplasia (either an advanced adenoma or carcinoma) with 0.6% having carcinoma. Factors conferring higher risk of further adenomas at surveillance are age greater than 60 years, male sex, and the presence of more than one adenoma at the initial procedure. The finding of more than 2 adenomas at initial examination increases the risk of advanced neoplasia at follow-up examination[32,61].

STRATIFICATION

Reported prevalence of adenomas ranges from 15%-40%, with advancing age and male sex associated with increasing prevalence. However, rates of adenoma detection may be as high as 50% in the general population when using modern "high definition" endoscopes[62,63]. Therefore the number of patients who could potentially be offered surveillance colonoscopy is substantial.

To avoid unnecessary, or "low yield", surveillance colonoscopies, it is necessary to identify those individuals with increased risk of CRC. This can be achieved through a risk stratification approach, as adopted by all the major current clinical guidelines (Tables 1-3).

Current guidelines vary in their definition of each risk group. However, there is consensus that individuals with one or two adenomas possessing no advanced features are classified as "low risk". At the opposite end of the spectrum, it is agreed that finding high grade dysplasia or greater than 10 adenomas confers a "high risk".

Current guidelines' variability in recommendations is due to the lack of good quality evidence to support surveillance strategy.

United Kingdom guidelines do not take account of polyp architecture, while guidance in the United States and Europe classifies individuals with a villous adenoma as "high risk".

Table 3 European Society of Gastrointestinal Endoscopy 2013[81]

The following recommendations for post-polypectomy endoscopic surveillance should be applied only after a high quality baseline colonoscopy with complete removal of all detected neoplastic lesions
In the low risk group (patients with 1-2 tubular adenomas < 10 mm with low grade dysplasia), the European Society of Gastrointestinal Endoscopy (ESGE) recommends participation in existing national screening programmes 10 yr after the index colonoscopy. If no screening programme is available, repetition of colonoscopy 10 yr after the index colonoscopy is recommended (strong recommendation, moderate quality evidence)
In the high risk group (patients with adenomas with villous architecture or high grade dysplasia or ≥ 10 mm in size, or ≥ 3 adenomas), the ESGE recommends surveillance colonoscopy 3 yr after the index colonoscopy (strong recommendation, moderate quality evidence). Patients with 10 or more adenomas should be referred for genetic counselling (strong recommendation, moderate quality evidence)
In the high risk group, if no high risk adenomas are detected at the first surveillance examination, the ESGE suggests a 5-yr interval before a second surveillance colonoscopy (weak recommendation, low quality evidence). If high risk adenomas are detected at first or subsequent surveillance examinations, a 3-yr repetition of surveillance colonoscopy is recommended (strong recommendation, low quality evidence)
The ESGE recommends that patients with serrated polyps < 10 mm in size with no dysplasia should be classified as low risk (weak recommendation, low quality evidence). The ESGE suggests that patients with large serrated polyps (≥ 10 mm) or those with dysplasia should be classified as high risk (weak recommendation, low quality evidence)
The ESGE recommends that the endoscopist is responsible for providing a written recommendation for the post-polypectomy surveillance schedule (strong recommendation, low quality evidence)

In a comparison of current United Kingdom and United States guidelines, it was found that following United Kingdom guidelines would better identify a group of patients at high risk of advanced neoplasia: those with ≥ 5 small adenomas or ≥ 3 adenomas including at least one of ≥ 10 mm. These patients would be offered a surveillance interval of 3 years according to United States guidelines or 1 year according to United Kingdom guidance. At one year follow-up, this group had an 18.6% risk of advanced neoplasia[64].

Conversely, patients with 1 or 2 small adenomas would be classified as low risk by United Kingdom guidelines regardless of histology. This group could be at relatively high risk if histology revealed advanced adenomas (HGD or villous architecture) and as such would be advised 3 year surveillance under United States guidelines. The same group of patients could have been offered no surveillance by following United Kingdom guidelines, but have a 7.1% absolute risk of advanced neoplasia at 1 year[64].

Current guidelines take account of findings at both the index and first surveillance colonoscopy in determining the second surveillance interval. This approach would be supported by a recent study showing that high risk features identified at either the index or first surveillance procedure increase the risk of advanced neoplasia at second surveillance[65].

SURVEILLANCE INTERVALS

High risk

The evidence to support the use of surveillance applies predominantly to the "high risk" group. The incidence of advanced neoplasia and carcinoma in these individuals is significantly increased at follow-up, and CRC mortality is reduced by their surveillance[33,59,60].

Data from the United Kingdom screening programme shows that in high risk individuals (by United Kingdom guidelines), the overall yield for advanced neoplasia at first surveillance (at 12 mo) was 6.6%, with a yield of 0.8% for CRC. These findings would support the current strategy of 12 mo surveillance in this group[66]. The same study found that villous architecture and a right-sided adenoma at the index procedure were associated with an increased risk of finding advanced neoplasia at 1 year follow-up. Therefore within the high risk group, there are other factors which could be used to further inform the appropriate surveillance interval for an individual.

Current United States guidelines classify patients with > 10 adenomas as highest risk. However, as only 0.1% of screening patients fall into this category, its clinical utility is limited.

Low risk

Within the low risk group, it is known that the absolute risk of advanced neoplasia at follow-up is low. Current guidelines are based on evidence that this group carries no increased risk of CRC compared to the general population[23,25]. A recent meta-analysis suggested individuals in the low risk group at the index procedure have a higher risk of advanced neoplasia at follow-up compared to those found to have no adenoma[67]. However, the absolute risk in both groups remains very low.

On the basis that the low risk group carry a risk of CRC equivalent to the general population, the guidelines advise surveillance at the interval prescribed by the relevant screening programme, *i.e.*, effectively advising no increased surveillance over that of the general population. The United Kingdom guidelines allow for deviation from this rule in that the low risk group may be offered no surveillance or a further procedure at 5 years. Of note, the United Kingdom NHS Bowel Cancer Screening Programme (BCSP), while following United Kingdom guidelines (BSG, 2010 and NICE, 2011), offers no surveillance in this group.

Recent data from Norway suggest a significant reduction in CRC mortality at 7.7 years in "low risk" patients after a single screening examination[68]. However, the definition of "low risk" used in this study

differs from that used in current guidelines as the study authors used cancer registry data and so did not have access to details of polyp size or number. Therefore, all patients with "multiple" polyps or with histology showing either villous architecture or high-grade dysplasia were classified as "high-risk". This definition makes comparison with other studies difficult.

Intermediate risk

Current guidelines differ most in recommendations for individuals with intermediate risk. It is in this group of patients that the benefit of surveillance is most uncertain.

Patients with 3 or 4 diminutive adenomas at index colonoscopy would be offered a surveillance procedure at 3 years according to United Kingdom, European, and United States guidelines. However, there is little evidence that this group of patients carries any significantly increased CRC risk compared to the general population.

There is evidence for the increased risk of identifying further adenomas at first surveillance in patients classified as intermediate risk at index procedure. However, the relative risk varies within this group of individuals dependent upon factors such as polyp size, patient age, and the presence of advanced adenoma at the index procedure, *i.e.,* with the varying definition of intermediate risk[69]. Evidence for an effect of surveillance on CRC incidence and mortality is lacking.

Serrated lesions

American and European guidelines include serrated polyps in their recommendations, which are not specifically dealt with in United Kingdom guidelines.

Serrated polyps are known to be more challenging to identify at colonoscopy and their predilection for the proximal colon is thought in part to explain the relatively lower protective effect of colonoscopy on incidence of right-sided CRCs[10].

Significant variability in detection of these lesions by endoscopists and their classification by pathologists has caused evidence on their natural history and risk profile to be lacking. However, further study and increased awareness of these lesions is likely to lead to further recommendations for surveillance in individuals found to have serrated polyps.

DISADVANTANGES AND LIMITATIONS OF SURVEILLANCE

At present, surveillance procedures account for 20%-30% of capacity in endoscopy departments: approximately the same proportion as primary screening procedures[70-73]. It is likely that demand for surveillance procedures will increase in line with more widespread implementation of screening programmes, rising adenoma detection rates associated with modern endoscopes and rising quality standards, and the increased recognition and surveillance of serrated lesions.

While colonoscopy is a generally safe procedure, there is a risk of major complications[74]. As such, the decision to proceed with surveillance colonoscopy must be informed by both the risk of CRC and the risk of a complication related to the procedure. Additionally, even an uncomplicated colonoscopy may represent considerable burden on the patient, who undergoes bowel preparation, time off work, and potential discomfort during the procedure. Fear of pain during the procedure is known to reduce the uptake of screening colonoscopy[75,76]. For surveillance programmes to be effective, uptake must be maximised. By definition, individuals invited for surveillance already have personal experience of colonoscopy. This experience is likely to inform the individual's decision on whether to undergo a surveillance procedure, highlighting the importance of patient experience during colonoscopy.

WHEN TO STOP SURVEILLANCE

The decision to discontinue surveillance is guided in current literature only on the criterion of the patient's chronological age[77]. It is known that rates of complications and post-procedure hospital admission are increased with advancing age and multi-morbidity. Advancing age also reduces the potential survival benefit in surveillance: as progression from adenoma to carcinoma is likely to take around 10 years, patients with a life expectancy of a similar or shorter time have little chance of benefit from a surveillance colonoscopy.

However, the use of chronological age alone is an over-simplification of the decision to discontinue surveillance: a decision which must balance the relative risks for the individual.

Patients found at their initial procedure to have an advanced adenoma, have a CRC risk similar to that of the general population after just one surveillance follow-up colonoscopy[23,59]. Further study is needed to identify more detailed criteria to guide the decision on continued surveillance.

ADHERENCE

There is strong evidence that adherence to current guidelines by physicians is highly variable[78]. Some surveillance procedures are performed earlier than advised, some late, and some not performed at all. Clinical guidelines are only a guide to clinicians and many will choose to advise a different approach for an individual patient.

Also, patients may choose not to be subjected to surveillance procedures for multiple reasons including their experience of colonoscopy and the perceived benefits of surveillance. The subject of patient choice

Table 4 Adenoma surveillance

Findings at index procedure	Suggested initial surveillance interval
No adenomas	No surveillance
1-2 adenomas with no advanced neoplasia	No surveillance
3-4 adenomas with no advanced neoplasia	3 yr
≥ 3 adenomas and advanced neoplasia	1 yr
≥ 5 adenomas	1 yr

in surveillance is an area requiring further study.

FURTHER STUDY

As discussed in the introduction to this paper, progression from adenoma to cancer usually occurs over many years. As such, the benefits of surveillance of colonic adenomas in reducing morbidity and mortality can only be realised over the long term. The introduction of surveillance programmes has become widespread only in recent years, so far limiting the available data on long-term follow-up. The known increased risk of CRC in patients found to have adenomas would make a randomised trial comparing surveillance to no surveillance unethical. Therefore, further study of the data from the era of widespread adenoma surveillance is needed to better inform future practice.

Current guidelines base recommendations on data collected prior to the widespread implementation of population screening programmes and prior to the use of robust quality metrics in colonoscopy. These factors may significantly alter the population classified within each risk group and so have a major impact on the outcomes of each group. More contemporary data from the era of high quality colonoscopy and population screening may allow more accurate risk stratification to better utilise limited colonoscopy resources in the future.

Future of adenoma surveillance

The Table 4 summarises suggested surveillance intervals based on current knowledge on risk stratification by polyp factors.

Polyp factors may be used, as in current guidelines, to determine surveillance interval. However, including other patient factors in this assessment may allow more accurate risk stratification. Possible factors include age, sex, family history of colorectal cancer, smoking status, or obesity.

Additionally, this combination of polyp and patient factors may further inform the decision on whether to continue with any further surveillance after the first surveillance procedure, as it is the first surveillance procedure that has greatest effect in reducing the future risk in the highest risk patients.

CONCLUSION

Internationally, increasing numbers of patients are embarking upon a course of surveillance colonoscopies due to the polyps discovered at the time of a previous examination. Each colonoscopy involves the burden of bowel preparation, potential anxiety and discomfort, and risk of complication for the patient. In many health settings, colonoscopy is a finite resource and so must be recommended only with a strong indication.

It is believed that individuals with non-advanced adenomas have no significantly increased risk of colorectal cancer compared to the general population. In addition, patients found at their initial procedure to have an advanced adenoma, have a CRC risk similar to that of the general population after just one surveillance follow-up colonoscopy[23,59].

As shown in this review, there is some retrospective evidence to support surveillance procedures in patients at the highest risk of CRC. For those at lower risk, further evidence is needed to better stratify risk and so inform discussions between the individual and their clinician on whether surveillance colonoscopy is appropriate.

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ESGE Days 2019 oral presentations / Saturday, April 6, 2019 14:30 – 16:00: CRC screening South Hall 1B

Bonnington, SN; Sharp, L; Rutter, MD

POST-POLYPECTOMY SURVEILLANCE IN THE ENGLISH BOWEL CANCER SCREENING PROGRAMME: RESULTS OF FIRST SURVEILLANCE + Playlist

ESGE Days 2019

April 04–06, 2019, Prague, Czech Republic

Chairman: Thierry Ponchon (France)

Newcastle University, Newcastle upon Tyne, United Kingdom
University Hospital of North Tees, Stockton on Tees, United Kingdom

Aims:

The English Bowel Cancer Screening Programme (BCSP) offers biennial g-FOBt from 60 – 74 years. Post-polypectomy surveillance is offered within BCSP during the screening age range for those at "high risk" (≥5 adenomas or ≥3 at least one ≥10 mm) and "intermediate risk" (3 – 4 small adenomas or at least one ≥10 mm).

CRC screening reduces mortality. To date, robust evidence to support post-polypectomy surveillance is lacking.

Methods:

Details were extracted from the BSCP database for individuals who attended surveillance from the start of the BCSP in 2006 until January 2017. Data were analysed using Stata 14. Advanced adenoma (AA) was defined as size ≥10 mm, ≥25% villous architecture, or HGD.

Results:

Results of first surveillance were available for 43088 individuals, of whom 51.9% were IR and 48.1% HR at baseline. The most advanced neoplasia detected at first surveillance is presented in the table. First surveillance was performed at the intended time interval (12 months for HR adenomas, 3 years for IR adenomas) in ≥89% of cases.

Tab. 1:

NAA = non-advanced adenoma

Most advanced histology at first surveillance	High risk at baseline (n = 20722)	Intermediate risk at baseline (n = 22366)	Difference between HR/IR
No adenoma	39.1% (n = 8112)	56.1% (n = 12567)	p 0.000
NAA	48.0% (n = 9963)	35.3% (n = 7904)	p 0.000
AA	12.3% (n = 2545)	8.0% (n = 1798)	p 0.000
CRC	0.5% (n = 102)	0.4% (n = 97)	p 0.120

Enlarge table

Subgroups : The subgroup with the lowest AA rate at first surveillance was those with one adenoma (≥10 mm) at baseline (n = 12397): 6.1% AA.

Conclusions:

CRC was diagnosed at first surveillance in a very small percentage of cases, reflecting the high quality baseline colonoscopy performed in the BCSP.

AA was found at first surveillance in 8.0% of those IR at baseline and in 12.3% of those HR at baseline. These results support the hypothesis that post-polypectomy surveillance may be safely delayed or discontinued in some groups, particularly those with one adenoma of ≥10 mm.

Source:

Bonnington S, Sharp L, Rutter M. POST-POLYPECTOMY SURVEILLANCE IN THE ENGLISH BOWEL CANCER SCREENING PROGRAMME: RESULTS OF FIRST SURVEILLANCE. Endoscopy 2019; 51(04): 116 - 116. doi:10.1055/s-0039-1681511

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Endoscopy 2019; 51(04): 138 - 138
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ESGE Days 2019 ePoster podium presentations / Friday, April 5, 2019 13:00 – 13:30: CRC screening 1 ePoster Podium 3

Bonnington, SN; Sharp, L; Rutter, MD

POST-POLYPECTOMY SURVEILLANCE IN THE ENGLISH BOWEL CANCER SCREENING PROGRAMME: RESULTS OF SECOND SURVEILLANCE + Playlist

ESGE Days 2019

April 04–06, 2019, Prague, Czech Republic

Chairman: Thierry Ponchon (France)

Newcastle University, Newcastle upon Tyne, United Kingdom
University Hospital of North Tees, Stockton on Tees, United Kingdom

Aims:

The English Bowel Cancer Screening Programme (BCSP) offers individuals aged 60 to 74 years guaiac FOB testing, with an invitation for colonoscopy if positive. Post-polypectomy surveillance is performed within the BCSP for individuals within the screening age range.

Methods:

Details were extracted from the BSCP database for individuals who attended surveillance from the start of the BCSP in 2006 until January 2017. Data were analysed using Stata 14.

Results:

9742 individuals with high risk (HR) adenomas at baseline subsequently attended for 2 nd surveillance (S2). In this group,

- Of 3639 with no further adenoma at 1 st surveillance (S1), 288 (7.9%) had advanced adenoma (AA) and 20 (0.5%) CRC at S2
- Of 3347 with LR adenomas at S1, 342 (10.2%) had AA and 9 (0.3%) CRC at S2
- Of 1533 with IR adenomas at S1, 217 (14.1%) had AA and 8 (0.5%) CRC at S2
- Of 1223 with HR adenomas at S1, 181 (14.7%) had AA and 5 (0.4%) CRC at S2

7822 individuals with IR adenomas at baseline attended S2.

- Of 4342 with no adenoma at S1, 203 (4.7%) had AA and 13 (0.3%) CRC at S2
- Of 2324 with LR adenomas at S1, 149 (6.4%) had AA and 7 (0.3%) CRC at S2
- Of 586 with IR adenomas at S1, 47 (8.0%) had AA and 1 (0.2%) CRC at S2

- Of 570 with HR adenomas at S1, 62 (10.9%) had AA and 1 (0.2%) CRC at S2.

Conclusions:

AA at S2 occurs in 7.9% – 14.7% for HR at baseline and 4.7% – 10.9% for IR at baseline. For those with a maximum risk of IR at both baseline and S1, AA occurs in ≤8.0% at S2. These findings support the discontinuation of surveillance in lower risk groups.

Source:

Bonnington S, Sharp L, Rutter M. POST-POLYPECTOMY SURVEILLANCE IN THE ENGLISH BOWEL CANCER SCREENING PROGRAMME: RESULTS OF SECOND SURVEILLANCE. Endoscopy 2019; 51(04): 138 - 138. doi:10.1055/s-0039-1681576

Endoscopy 2019; 51(04): 153 - 154
DOI: 10.1055/s-0039-1681622

ESGE Days 2019 ePoster podium presentations / Friday, April 5, 2019 14:00 – 14:30: CRC screening 3 ePoster Podium 3

Bonnington, SN; Sharp, L; Rutter, MD

POST-POLYPECTOMY SURVEILLANCE IN THE ENGLISH BOWEL CANCER SCREENING PROGRAMME: MULTIVARIATE LOGISTIC REGRESSION OF FACTORS INFLUENCING ADVANCED ADENOMA DETECTION AT FIRST SURVEILLANCE + Playlist

ESGE Days 2019

April 04–06, 2019, Prague, Czech Republic

Chairman: Thierry Ponchon (France)

Newcastle University, Newcastle upon Tyne, United Kingdom
University Hospital of North Tees, Stockton on Tees, United Kingdom

Aims:

The English Bowel Cancer Screening Programme (BCSP) offers individuals aged 60 to 74 years guaiac FOB testing, with an invitation for colonoscopy if positive. Post-polypectomy surveillance is performed by quality-accredited colonoscopists within the BCSP for individuals within the screening age range.

Methods:

Details were extracted from the BSCP database for 41519 individuals who attended surveillance (in the intermediate or high risk category) from the start of the BCSP in 2006 until January 2017. Data were analysed using Stata 14. Multivariate logistic regression was performed for the outcome of advanced adenoma (AA) at first surveillance, defined as size ≥10 mm, ≥25% villous architecture, or high-grade dysplasia (HGD).

Considered in the analysis were person factors: gender, age, smoking status, alcohol intake, BMI, co-morbidity; and procedure factors: quality of examination, number of adenomas, size of largest adenoma, villous architecture, HGD, proximal location, piecemeal resection, and surveillance interval.

Results:

The multivariate odds ratio (OR) for baseline factors found to have statistical significance are presented below.

Male gender; OR 1.13 (p0.001.)

Suboptimal examination*; OR 1.46 (p0.000).

Total number of adenomas (multiplicity):

1 OR 1

2 OR 1.56 (p0.000)

3 OR 1.58 (p0.000)

4 OR 1.90 (p0.000)

5 OR 2.24 (p0.000)

6 – 9 OR 2.47 (p0.000)

≥10 OR 3.03 (p0.000)

Maximum villous architecture:

TA OR 1

TVA OR 1.37 (p0.000)

VA OR 1.70 (p0.000)

Non-pedunculated adenoma ≥10 mm; OR 1.38 (p0.000)

Current smoker; OR 1.16 (p0.001)

Alcohol intake ≥15 units/week; OR 1.09 (p0.010)

ASA grade # :

1 OR 1

2 OR 1.09 (p0.019)

3 – 5 OR 1.33 (p0.000)

(*Suboptimal defined as either poor bowel prep and/or incomplete to caecum.

American Society of Anaesthesiologists grade).

Conclusions:

The only factor with an OR > 2 was adenoma multiplicity at baseline. These findings will help inform future surveillance algorithms.

Source:

Bonnington S, Sharp L, Rutter M. POST-POLYPECTOMY SURVEILLANCE IN THE ENGLISH BOWEL CANCER SCREENING PROGRAMME: MULTIVARIATE LOGISTIC REGRESSION OF FACTORS INFLUENCING ADVANCED ADENOMA DETECTION AT FIRST SURVEILLANCE. Endoscopy 2019; 51(04): 153 - 154. doi:10.1055/s-0039-1681622

PTH-014 POST-POLYPECTOMY SURVEILLANCE IN THE ENGLISH BOWEL CANCER SCREENING PROGRAMME: A PROSPECTIVE COHORT STUDY, PRELIMINARY RESULTS

[1,2]Stewart Bonnington*, [2]Linda Sharp, [1,2]Matt Rutter. [1]*North Tees and Hartlepool NHS Trust, Stockton-on-Tees, UK*; [2]*Newcastle University, Newcastle Upon Tyne, UK*

10.1136/gutjnl-2018-BSGAbstracts.36

Introduction The English Bowel Cancer Screening Programme (BCSP) offers individuals aged 60 to 74 years guaiac FOB testing (gFOBt), with an invitation for colonoscopy if positive. Of more than 3 00 000 individuals who have attended for colonoscopy, over 45 000 attended post-polypectomy surveillance (PPS) after having intermediate (IR) or high risk (HR) adenomas detected and resected at screening. It is established that screening reduces mortality from colorectal cancer (CRC). However, robust evidence to support PPS is lacking.

Methods Details were extracted from the BSCP database for individuals who attended PPS from the start of the BCSP in 2006 until 3/1/2017. Data were analysed using Stata 14.

Results 67,435 PPS episodes were performed in 45 151 individuals. 60% of individuals had attended only 1 PPS episode, 34% attended 2, 5% attended 3, and 0.4% attended 4 or 5.

PPS episodes per year greatly increased over the study period. In 2008, 453 episodes were attended, rising to 13 698 in 2016 (figure 1).

70% of those attending PPS were male. 44% were aged 60–64 at the time of index screening, 43% aged 65–69, and 10% aged 70–74. The oldest age group had a higher proportion (68%) of HR individuals than in the younger groups.

Screening risk category varied with gender. Overall, 40% of females and 51% of males were HR (figure 2).

Overall, the findings at first PPS demonstrate a high proportion of individuals with no further adenoma found (table 1).

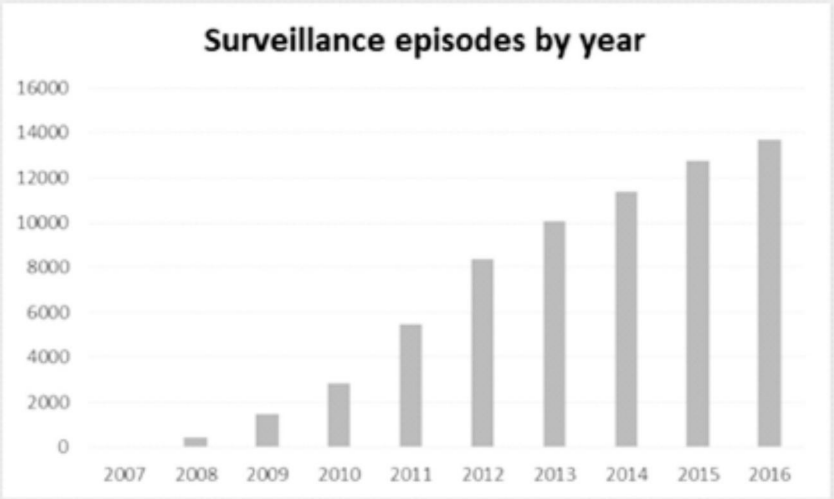
Conclusions PPS accounts for an increasing proportion of endoscopy workload in the BCSP and more broadly in the UK and internationally. These results demonstrate a low proportion of CRC or IR or HR adenomas diagnosed at PPS in the BCSP.

Individuals with HR adenomas at screening more often had further adenomas detected at first PPS when compared to those with IR adenomas at screening. HR individuals also had a higher probability of IR or HR adenomas at first PPS. CRC diagnosis at first PPS was low in both groups (≤0.5%).

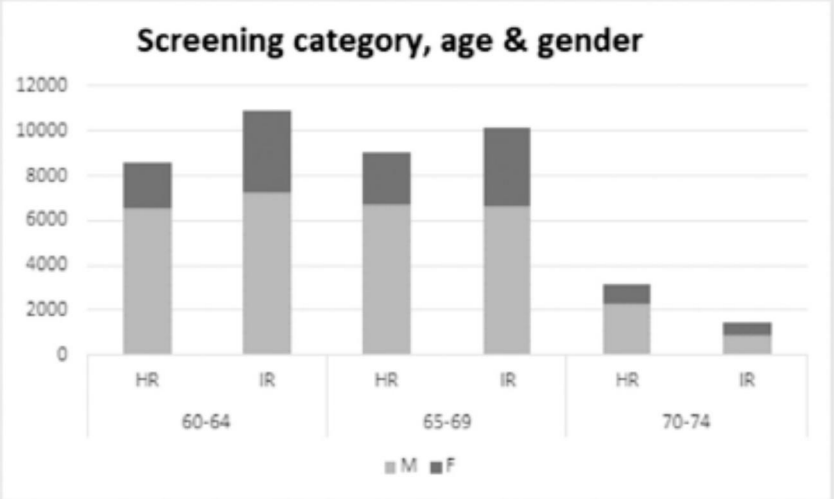
Further evaluation of the BCSP database is ongoing in order to identify subgroups most likely to benefit from PPS.

Abstract PTH-014 Table 1 Outcome of 1st PPS episode, by risk group at screening

Outcome of 1 st PPS		No adenoma	LR	IR	HR	CRC
HR at screening	**proportion** (95% CI)	**0.39**	**0.37**	**0.15**	**0.08**	**0.005**
		(0.386–0.399)	(0.366–0.379)	(0.145–0.155)	(0.075–0.082)	(0.0039–0.0058)
	n	8225	7821	3161	1651	102
IR at screening	**proportion** (95% CI)	**0.56**	**0.32**	**0.08**	**0.03**	**0.004**
		(0.555–0.568)	(0.317–0.329)	(0.073–0.080)	(0.030–0.035)	(0.0036–0.0053)
	n	12 869	7422	1766	755	100



Abstract PTH-014 Figure 1 Surveillance episodes by year



Abstract PTH-014 Figure 2 Screening category, age & gender

Durham University
School of Medicine, Pharmacy and Health

Shaped by the past, creating the future

Dr David Ekers
Clinical Senior Lecturer
Chair, School of Medicine, Pharmacy and Health Ethics Sub-Committee

Dr Stewart Bonnington
School of Medicine, Pharmacy and Health
Durham University

12th February 2016

Dear Stewart

Re: Ethics Application ESC2/2016/MSC01 - Surveillance of colonic polyps – stop criteria

Thank you for sending the above application to the School of Medicine, Pharmacy and Health Ethics Sub-Committee for proportionate ethical review. I reviewed this project as Chair of the committee. The project is an evaluation and review by the full committee is therefore not required. No significant ethical issues were identified, and I am pleased to confirm Durham University ethical approval for the evaluation.

This approval is given on the following basis:

- That data generated for this study is maintained and destroyed as outlined in this proposal and in keeping with the Data Protection Act.
- If you make any amendments to your study, these must be approved by the committee prior to implementation.
- At the end of the study, please submit a short end of study report (ESC3 form) to the School ethics committee.

Please do not hesitate to contact me should you have any questions. Good luck, I hope that the evaluation goes well.

With best wishes

Dr David Ekers

NHS
Bowel Cancer Screening Programme
Research Committee

John Scholefield
Chair

C/o NHS Cancer Screening Programmes
Fulwood House
Old Fulwood Road
Sheffield
S10 3TH

Tel: 0114 2013040

rachel.athorn@phe.gov.uk

Dr Stewart Bonnington & Professor Matthew Rutter,
University Hospital of North Tees and Durham University.

snbonnington@doctors.org.uk
Matt.rutter@nth.nhs.uk

21st October 2015

Dear Dr Stewart Bonnington & Professor Matthew Rutter,

The Bowel Cancer Screening Programme (BCSP) Research Committee met on 16th October 2015 to discuss your project plans: *Stop surveillance criteria – BONNINGTON / RUTTER - ID 158*

The Committee gave their support to the project, but requested further clarification on what your plans are with the shared decision making.

As a condition of support, the BCSP Research Committee requires you to keep them informed of developments with the project, including any changes of status, any significant adverse events, when completed, and when written up.

Any applications requiring patient identifiable data and/or potentially identifiable data from the BCSP programme will also require PHE ODR (Office of Data Release) approval. The ODR was established in January 2014 as a cross-agency service to manage the release of explicitly identifiable or potentially identifiable data from PHE. The ODR provides systematic, consistent and coherent approach to the review of data release requests for PHE datasets, to ensure that there is a legal and legitimate purpose for processing personal confidential data and that any risk of disclosure is minimised. Requests for data can be made by emailing ODR@PHE.gov.uk

The BCSP Research Committee requires you to notify them promptly of any incidents that would be recorded on the National Research Ethics Service (NRES) Breaches Register. Undertaking research within the Screening Programme following receipt of this letter of support assumes your agreement to fulfil this obligation. NRES has the potential to share information with the BCSP Research Committee regarding any breaches of ethics related to projects involving the BCSP.

The Committee wishes you well with your project.

Yours sincerely

Rachel Athorn MSc BMedSci
On behalf of the NHS BCSP Research Committee.

Data Sharing Contract

Public Health England

Part 1: Front Sheet

ODR Reference	ODR1516_447
Title	**Colonic adenoma surveillance: stop criteria.**

1 Parties

This Contract is made between:

1.1 **Public Health England, an Executive agency of the Department of Health ("PHE"), of Wellington House, 133-155 Waterloo Road, London SE1 8UG, United Kingdom**; and

1.2 The party whose details are set out below (**"Data Recipient"**):

Name:	Stewart Bonnington on behalf of:
Organisation or Company (including company number if	North Tees and Hartlepool NHS Foundation Trust
Department	Gastroenterology
Address:	University Hospital of North Tees Hardwick Road Stockton-on-Tees TS19 8PE

2 Term of this Contract

2.1 This Contract shall commence on the Start Date specified in the table below and shall continue, unless terminated earlier in accordance with the terms of this Contract (Section 13) until the End Date in the table below.

Start Date	09/11/2016	***End Date***	08/11/2017
Term:	12 months		

3 Status of this Contract

3.1 This Data Sharing Contract (**Contract**) comprises this Part 1 (Front Sheet), Part 2 (Terms and Conditions) and Part 3 (Purpose – including objectives for processing, Special Conditions, Approved Project Documentation, Data Specification and where applicable Permitted Users). It sets out the terms on which the PHE agrees to share the Data with the Data Recipient.

3.2 The purpose of this Contract is to:

3.2.1 clarify the responsibilities and commitments of the parties in relation to the Data;

3.2.2 impose confidentiality requirements on the Data Recipient;

3.2.3 outline the data security principles and requirements with which the Data Recipient must comply;

3.2.4 set out the audit rights of PHE; and

3.2.5 include arrangements for termination of this Contract.

By signing this Part 1, the parties agree to be bound by the terms of this Contract.

Signed for and on behalf of the Data Recipient:	
Organisation Name:	North Tees + Hartlepool NHS FT
Signature:	
Name:	
Position in organisation:	
Date:	13/12/16

Signed for and on behalf of the Public Health England:	
Name:	Mat Jordan
Signature:	
Role:	IT Strategy & Ops Manager
Date:	21 December, 2016

Signed for and on behalf of the Public Health England Office for Data Release:	
Name:	Tariq Malik
Signature:	Digitally signed by Tariq Malik DN: cn=Tariq Malik, o=PHE, ou=DDR, email=tariq.malik@phe.gov.uk, c=GB Date: 2016.12.22 165353 Z
Role:	
Date:	

Public Health England

Office for Data Release
Public Health England
Skipton House
80 London Road
London
SE1 6LH

T +44 (0) 20 7654 8030

www.gov.uk/phe

Dr Stewart Bonnington
Gastroenterology Department
University Hospital of North Tees
North Tees and Hartlepool NHS Foundation Trust
Hardwick Road
Stockton-on-Tees
TS19 8PE

27/10/2017

ODR contract reference:	ODR1516_447
Amendment reference:	A2
Application title:	Colonic adenoma surveillance: stop criteria

Dear Dr Bonnington,

Please accept this letter as acknowledgement of your amendment request(s) to Data Sharing Contract ODR1516_447.

Summary of request(s):

1. The Data Recipient is requesting the following data items to be released as part of the National Bowel Screening Programme work programme to support the Colonic adenoma surveillance: stop criteria project:
    - SUBJECT_EPIS_ID
    - SCREENING_SUBJECT_ID
    - EXT_TEST_ID
    - POLYP_ID
    - POLYP_HISTOLOGY_ID
    - POLYP_W_GTR_1_HISTOLOGY_REC
    - Secondary Piece

2. The Data Recipient is also requesting the existing Data Sharing Contract to be renewed for 12 months to continue with the planned work.

Outcome of ODR review

The ODR is satisfied with the justification provided to amend this Contract and can accommodate, subject to the conditions outlined below, the following changes:

1. Enhancement of the data specification with additional variables (described in Annex 1)
2. Extension of the term of contract.

Conditions of approval:

Due to upcoming changes to data protection legislation, the term of the extension will be limited to **31/03/2018**.

Notice of planned contract novation

In May 2018, the UK will implement legislation to comply with the EU General Data Protection Regulation (GDPR) – the new legal framework for data protection in the EU.

In preparing for the introduction of the GDPR, the ODR will be reviewing and updating the terms and conditions in our data sharing contract to ensure that there are adequate contract provisions in place which will, come May 2018, comply with these new requirements, including:

- reflecting the revised definitions in the GDPR, and;
- revised timelines for reporting breaches to the Information Commissioner's Office.

Over the coming months, the ODR will be in touch with you with a new data sharing contract, which reflects these updated terms and conditions. At this point, we will also reflect your request to extend the term of your data sharing contract to **25/10/2018**, should this still be required.

These changes outlined above will be effective from the date of this correspondence. The terms and conditions of the Contract will otherwise remain unchanged.

PHE Screening will be in contact with you regarding the extraction and disclosure of the agreed dataset in due course.

Yours sincerely,

Office of Data Release
E: ODR@phe.gov.uk

Public Health England

Office for Data Release
Public Health England
Skipton House
80 London Road
London
SE1 6LH

T +44 (0) 20 7654 8030

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Dr Stewart Bonnington
Gastroenterology Department
University Hospital of North Tees
North Tees and Hartlepool NHS Foundation Trust
Hardwick Road
Stockton-on-Tees
TS19 8P

13 March 2018

ODR contract reference:	ODR1516_447/B
Application title:	Colonic adenoma surveillance: stop criteria

Dear Dr Bonnington,

I can confirm that your amendment (ODR1516_447/A3) to access depersonalised data from the NHS Bowel Cancer Screening Programme has been conditionally approved by the Office for Data Release (ODR) subject to the PHE standard conditions of approval.

Conditions of approval:

1. Execution of a GDPR compliant data sharing contract between the parties.
2. Payment of the full economic cost to prepare and release the data in line with the terms of Clause 10 ("Charges") of your licence. The costs attributable to this project are outlined below.

Charge(s):

Service	Cost (exc VAT)
Contract execution and administration by the ODR	£0.00
Data preparation, extraction and quality assurance of NHS Bowel Cancer Screening (mortality) data specified in data transfer form (Annex A) – Table 12	£0.00
Total	£0.00

Next steps:

Should you wish to proceed with your application, please return the following documents at your earliest convenience to odr@phe.gov.uk quoting your ODR reference number in the subject field:

1. An electronic copy of the project-specific data sharing contract [ODR1516_447/B] signed by your organisation. This contract stipulates the permitted processing activities, alongside the terms and conditions of the data release. *A copy of the contract accompanies this letter.*

On receipt of this information, the application for data will be approved and the activity to support data preparation and extraction commenced in line with the detailed specification documented in Annex A (Data Transfer Form).

To discuss any of these requirements, please contact the ODR by email, ODR@phe.gov.uk, or on 020 7654 8030.

Yours sincerely,

Rachel Crowther
Research & Evaluation Coordinator
Office of Data Release
E:ODR@phe.gov.uk

Data Sharing Contract

Public Health England

Part 1: Front Sheet

ODR	ODR1516_447/B
Title	Colonic adenoma surveillance: stop criteria.

Parties

This Contract is made between:

Public Health England, an Executive agency of the Department of Health ("PHE"), of Wellington House, 133-155 Waterloo Road, London SE1 8UG, United Kingdom;

And;

The party whose details are set out below ("Data Recipient"):

Name:	Stewart Bonnington on behalf of
Organisation or Company (including company number if relevant):	North Tees and Hartlepool NHS Foundation Trust
Department	Gastroenterology
Address:	University Hospital of North Tees Hardwick Road Stockton-on-Tees TS19 8PE

Term of this Contract

This Contract shall commence on the Start Date specified in the table below and shall continue, unless terminated earlier in accordance with the terms of this Contract (Clause 13) until the End Date in the table below.

Start Date	09/03/2018	*End Date*	08/03/2019
Term:	12 months		

Status of this Contract

This Data Sharing Contract (Contract) comprises this Part 1 (Front Sheet), Part 2 (Terms and Conditions) and Part 3 (Purpose) – including Objectives for Processing, Special Conditions, Approved Project Documentation, and where applicable Permitted Users, the Schedules and Approval Letter(s). It sets out the terms on which PHE agrees to share the Data with the Data Recipient.

This Contract sets out the legally binding terms and conditions that will apply to each and every occasion PHE agrees to share data with the Data Recipient for the Purpose. It addresses any residual privacy risks and documents the actions taken to identify, address and mitigate those risks wherever possible.